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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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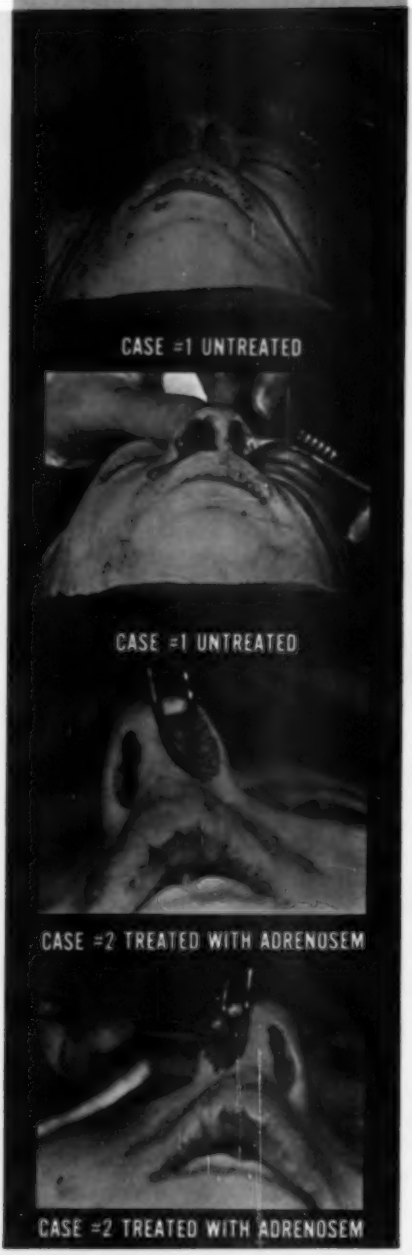

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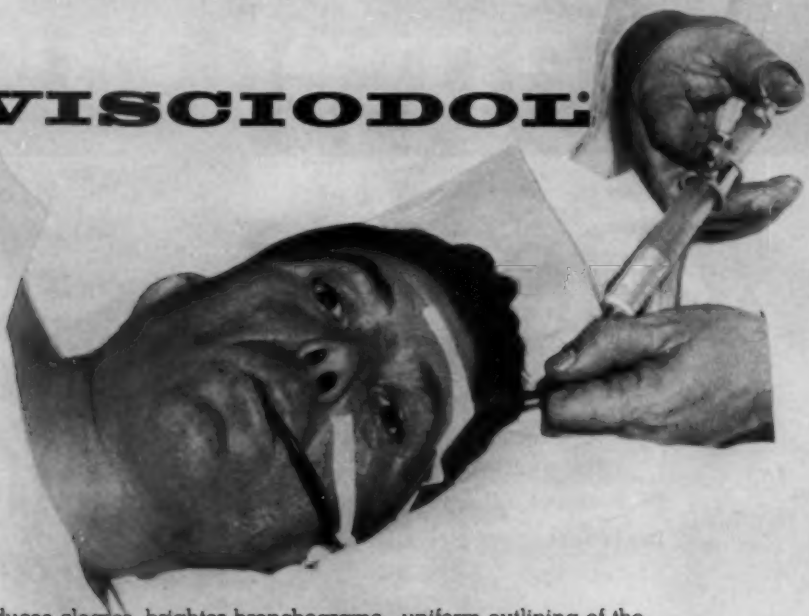

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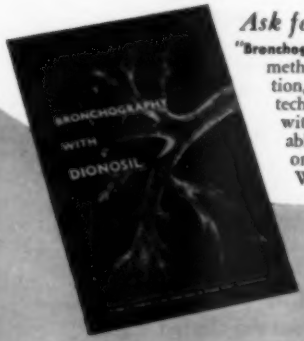

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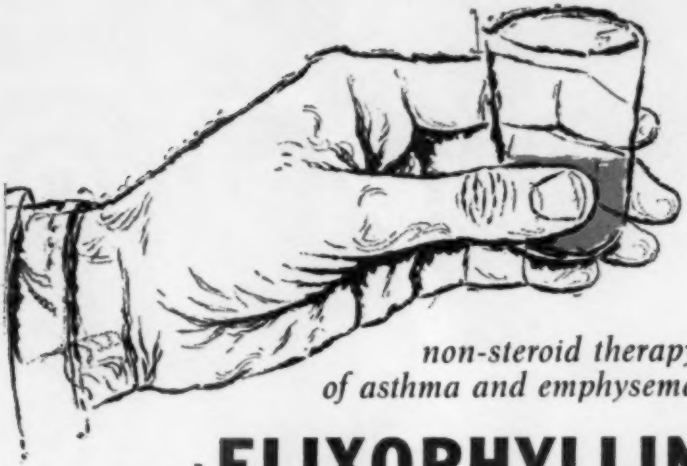

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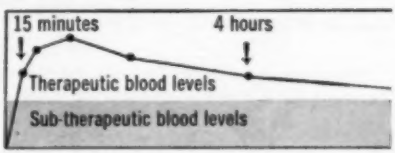

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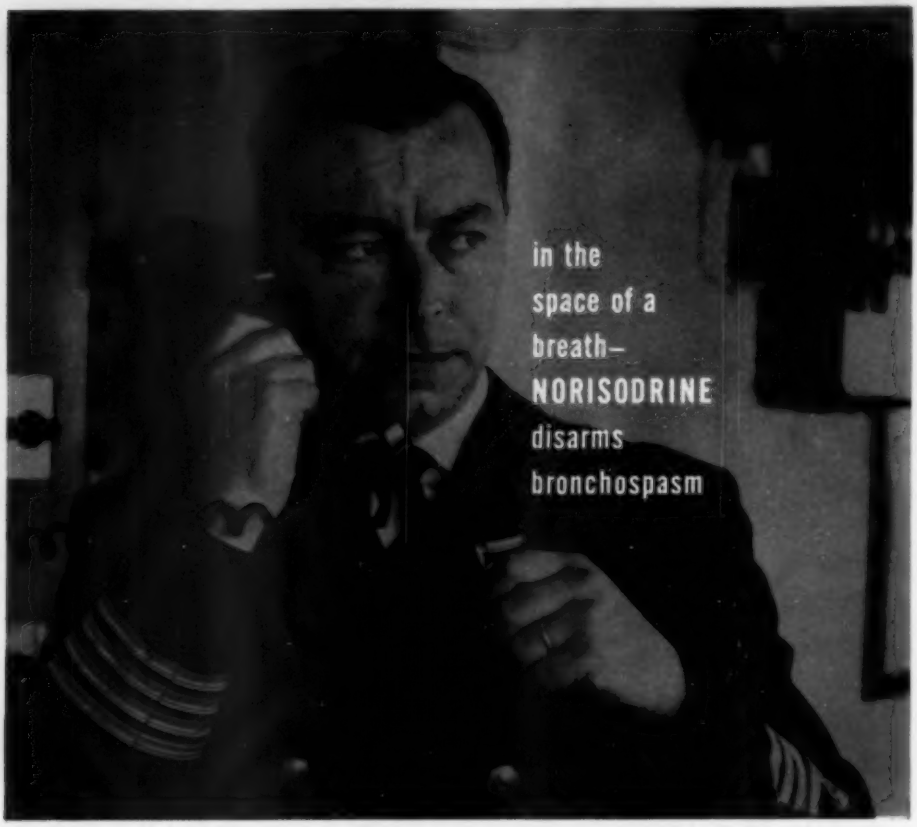

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THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES

VOLUME 78 | *October 1958* | NUMBER 4

THE J. BURNS AMBERSON LECTURE[1]

The Supporting Structure of Immunity in the Therapy of Tuberculosis

ESMOND R. LONG[2]

(Received for publication May 20, 1958)

"The tendency to recovery in some patients is so marked that it ensues in spite of the most injurious treatment."

LAWRASON BROWN (1).

The Amberson Lecture, named for a distinguished physician who has contributed much to the understanding of tuberculosis, provides an opportunity, in the midst of a mass of technical exposition, to review recent advances in tuberculosis control in the light of a long and crowded past. Few diseases have excited so much investigation. Not many have been so conspicuous for the optimism that has greeted each advance. In few, on the other hand, has there been such occasion to marvel at the satisfaction in one era over what seemed like meager accomplishment to the next one.

In a recent tour of Veterans Administration hospitals, while admiring the therapeutic successes that have become almost routine, I was impressed by a not inconsiderable number of treatment failures, and at the same time astonished by occasional favorable progress in patients who refused adequate treatment and seemed to do everything possible to impede their own recovery.[3]

There was nothing new in the observation. All physicians are aware of the variability of individual response to treatment. But I could not escape the feeling that it may be salutory at times, in the midst of success with new therapies, to re-stress the fact that, different as therapeutic regimens have been in the long history of tuberculosis control, certain personal factors in

[1] Founded and sponsored by physicians of the Bellevue Hospital Chest Service, New York, New York. The Amberson Lecture will be delivered each year at the annual meeting of the National Tuberculosis Association and its medical section, the American Trudeau Society.

[2] Pedlar Mills, Virginia.

[3] At this point, slides of roentgenograms from the Tucson Veterans Administration Hospital were shown, illustrating: (*1*) standard treatment and successful outcome, (*2*) standard treatment and unsuccessful outcome, and (*3*) inadequate treatment in a wholly uncooperative patient and favorable outcome.

patients are vital in the success or failure of their treatment, regardless of the nature of the therapy.

What to call the element in a patient's makeup that gives him a better chance for recovery than his fellow patients, irrespective of his treatment, is hard to define. For want of a better designation, I have used a very poor one, *immunity*, recognizing that it is an all-or-none word, that people are immune or not immune, and that a better label should be used. The word *resistance* is not suitable, for it has acquired too many different connotations.

Under the designation immunity I propose to include all those attributes, native or acquired, which make for resistance to the inroads of tuberculosis regardless of factors of treatment. Native and acquired immunity are probably only two phases of the same phenomenon; persons most readily immunized seem to be those who have a good start in that direction in the first place.

What I intend to say is partly covered by one of the "Tuberculosis Theses" of a revered leader of former days, Lawrason Brown, who had an extraordinary gift for pithy expression, which he voiced in "Rules for Recovery," "Theses," and the like. Brown said "The tendency to recovery in some patients is so marked that it ensues in spite of the most injurious treatment." (1). At about the same time, Allen Krause (2) wrote "Fortunately not all tuberculosis is continuously progressive. Indeed it is only the rare cases which are."

Tuberculosis is a disease that has always been characterized by an astonishingly optimistic individual outlook even in the face of a statistically poor prognosis for tuberculous patients as a whole. Up to recent times advanced tuberculosis was a truly fatal ailment. A well-known study at one of our leading sanatoriums a generation ago disclosed a mortality in cavitary cases of 80 per cent within a year of admission, 90 per cent within five years, and 95 per cent within a fifteen-year period (3). The high fatality in advanced cases, as compared with the observed frequent recovery in minimal cases, suggests that a golden period had been neglected between the minimal and moderately advanced stages in those who died. At the same time one cannot avoid a lurking suspicion that the actual situation might have been somewhat different, and that for some people, i.e., the very ones who died of advanced disease, even minimal tuberculosis was a fatal affection proceeding inexorably to advanced disease with the high fatality we have noted. Put another way, the patients with advanced disease, for whom such a high rate of fatality was demonstrable, might in many cases have represented not so much persons whose disease was neglected in its minimal stage as persons who, in contrast to the majority of our population, were constitutionally unable, temporarily at least, to resist even the initial inroads of the disease.

Whatever the facts, it is certain that in each of the successive periods of varying therapy a good deal of satisfaction has prevailed in the advances made over the therapy of the past. It has seemed to me that it might be of some interest, with this fact in mind, to review some of the methods of treatment in vogue within the period covered by our own National Tuberculosis Association.

Climate in the Treatment of Tuberculosis

In the closing years of the last century, a system of combined therapy was in practice, the basic regimen of which was climate and exercise. It had developed slowly over decades—centuries in fact—during which all sorts of other treatments were practiced, and was a somewhat late successor to an almost ferocious period of bleeding, purging, and blistering for this debilitating disease. Some people recovered even under the latter therapy—perhaps it would be fair to say in spite of it—but treatment failures were far more numerous. Survival was indeed the exception, but enough persons did recover to encourage their physicians in the soundness of the treatment prescribed.

The therapy of climate was looked upon by the bulk of the medical profession in the late years of the nineteenth century as more rational, however, and supported by the experience of centuries. An immense amount of argument took place over the merits of different climates, and, with the lack of controlled studies, professional authority and individual preference were generally the deciding factors. By and large the trend was toward high and dry places, and many serial case studies were published to document the virtues of one or another region. Citation of these would be tedious. A few personal reminiscences from the experience of friends of all of us might be equally illuminating and more interesting.

Many of us recall the case of Henry Sewall, one of our past presidents, who did much to advance our cause. Sewall broke down with bacteriologically proved tuberculosis in the late eighteen eighties. One of his teachers, the celebrated physiologist, Newell Martin of the Johns Hopkins Medical School, acting as Sewall's vocational counselor, wrote to Sewall: "Do you not think it is your duty to give up all Baltimore work and go at once to Colorado to start life there either as a doctor or ranchman. If you do that," he went on to say, "you may live for years; if you stay in Baltimore it will probably be a matter of a year or two." (4).

Sewall went to Denver in 1890, chose the life of a doctor rather than that of a rancher, and practiced medicine and occupied the university chair of physiology while he "cured." He reached his "target point" of restoration to health in due course and lived nearly fifty years after his migration, a beloved figure not only in the state of his adoption but throughout the country. He made many scientific studies of climate and believed fully in its value, but retained a conservative attitude. I can remember, at a meeting of the state medical society, his quiet squelching of a young and vigorous physician who maintained stoutly that, although some cases of tuberculosis might progress in Colorado after contraction elsewhere, none ever originated within the boundaries of the state.

This is only one of countless cases that could be cited. Not everyone was so fortunate as Sewall, even with exactly the same treatment, i.e., climate with a modicum of rest and a normal life otherwise. It may be that the biologic systems of Sewall and the others who recovered possessed some ingredient not granted to those who progressed from bad to worse and failed to survive.

In any event, a good many did recover as an apparent result of climatic therapy, and physicians recorded their success with growing complacency.

All this time there was much argument over the role of exercise. Horseback riding was the traditional recommendation of the exercise school. A respected American physician (5), whose advice was widely followed, had written that vigorous exercise and free exposure to the air were by far the most effective remedies in pulmonary consumption. In his opinion, daily and long-continued riding on horseback, or in carriages over rough roads, constituted the most effective type of exercise. Some virtue was attributed to the shaking up and, indeed, for some recalcitrant patients who simply would not follow medical advice, special jolting chairs and joggling boards were contrived so that they could take treatment at home on an ambulant basis rather than in the prescribed form on the back of a horse.

The related form of therapy, following the horse in the more solid comfort of an upholstered carriage, in the opinion of many was a safe compromise between the regimens of rest and exercise. The classic case history of Nathaniel Bowditch was related with inimitable charm by James J. Waring in the first of the Amberson lectures (6).

At any rate, with or without exercise, the number of cures attributed to climate and its adjuncts grew, and so did the confidence of tuberculosis specialists. Although records are not available to prove it, certainly more patients recovered on both the climate-exercise and climate-rest therapeutic regimens than on the old combined therapy of bleeding, blistering, and purging. Unquestionably there remained a hard core of treatment failures—indeed a big one—but it was not large enough to overcome the optimism of the medical profession in the light of an improving trend.

At about this time heavy alimentation was an important part of the prescription of many experienced physicians. A conventional protocol was three or four quarts of milk and a dozen eggs a day, besides the usual three square meals—a formidable task for some patients, but one that a few of us can recall as not impossible. Later this treatment, like vigorous exercise, fell into disrepute; but even as sound a physician as Lawrason Brown, who derided excess in alimentation, wrote, "Give your patient as little food as will serve his purpose, and have clearly in mind what this purpose should be: to gain up to ten to twenty pounds beyond his usual weight." (1).

The climatic treatment finally stabilized on a sanatorium basis, with emphasis on fresh air and good food, with rest rather than exercise as the major adjunct to the benefits of climate. The sanatoriums were located, as has been emphasized over and again, in places of difficult accessibility. But plenty of evidence was adduced in support of their sites. The Medical Advisory Board of the National Jewish Hospital in Denver, in an exhaustive study (7), pointed out that the Army, Navy, and Public Health Service of the U. S. Government, as well as large fraternal and religious bodies, consistently placed their sanatoriums in regions with a reputation as health resorts, following, in that respect, the traditions of Brehmer, Dettweiler, and Trudeau.

The sanatorium movement took away much of the age-old hit-or-miss element of tuberculosis practice. It was on too small a scale for some years to make much of a dent in the mass tuberculosis problem, but was soon accepted as the ideal measure for tuberculosis therapy for those who could afford it. For those who could not, it was simulated through tents, sleeping porches, window boxes, and the like, at home. Physicians, public health workers, and statisticians agreed that, thanks to the new institution, the sanatorium, chances for permanent arrest of the disease were better than ever before. The usual hard core of cases, however, in which progress of the disease appeared inexorable, was evident. But the hard core appeared to be growing smaller. Once the rule had been to die of the disease sooner or later; now the chances of not dying of it, at least for a long time, were better and better. Astonishing recoveries occurred in some cases on prolonged rest; many of these were re-treatment cases, in which a previous experience with either the simple climatic cure or exercise therapy had failed. At the same time a steadily growing percentage of original treatment cases were in the sanatoriums.

The major element in therapy was now avowedly rest—the "sovereign remedy," Allen Krause (2) called it, stressing it over and over again in his authoritative dissertations as the most important in the sanatorium trinity of rest, fresh air, and good food. Others listed the elements in a slightly different sequence—Sir Robert Philip (8) called free exposure to open air the one essential in treatment, and built his celebrated home-treatment plan upon it. Surgical as well as pulmonary tuberculosis was believed to respond miraculously to the effect of open air. The "Rollier system" will be recalled by everyone. No report of the success of modern chemotherapy has surpassed the glowing account, in the first volume of the *Transactions* of the National Tuberculosis Association, of open air in the treatment of bone tuberculosis, by the distinguished Baltimore surgeon, W. S. Halsted (9), one of the founders of modern medicine in this country.

But the great majority, while granting the synergistic effect of the other two, banked solidly on rest, which at some stage in the treatment meant bed rest. This was looked upon as positive therapy, not mere relief from fatigue, and was measured out in doses like an antimicrobial drug. Lawrason Brown (10) wrote of it: "There are three great remedies in the treatment of tuberculosis, medicines which when rightly used are far superior to those found in any pharmacopoeia: rest, food, and fresh air." In his view, the latter two were useless without the first of these. He and hundreds of other writers cited case after case in which absolute rest had turned the tide when everything else failed. He, too, however, was forced to admit the possibility of an innately low resistance in some persons, and in retrospect one can only wonder if this devoted crusader was not himself an example of it.

Collapse Therapy

When collapse therapy came in, it was at first rationalized as an additional type of rest. Later, various physiologic side effects, such as lessened circulation

and carbon dioxide accumulation, were considered as contributing to its good results. Pneumothorax has been replaced to such an extent by the antimicrobial treatment of the present period that it is becoming difficult to remember the satisfaction with which the procedure was viewed a few years ago. The opening words of John Alexander's *Collapse Therapy of Pulmonary Tuberculosis* (1937) (11), may be recalled:

> Collapse therapy, the only important addition to the treatment of pulmonary tuberculosis since the sanatorium was introduced fifty years ago, has revolutionized the management of phthisis. Collapse therapy offers a majority of tuberculous patients an excellent chance of becoming completely well. An era of hope as to the curability of active cavernous pulmonary tuberculosis has succeeded decades of resignation or false optimism on the part of both physicians and patients during the years when the sanatorium regimen was their only weapon.

In the same volume John Barnwell noted in his well-known conservative way that as a therapeutic procedure pneumothorax had gained steadily in approval, slowly at first, rapidly in later decades with improvement in methods. With all facts in mind, however, he found it wise to warn of the danger of overenthusiasm for the method. Attention had been drawn repeatedly to the limitations of the procedure, and perhaps never with greater precision than by a committee first appointed by J. Burns Amberson as chairman of the Clinical Research Committee of the American Sanatorium Association. This committee, reporting in 1935 (12), after noting a steady increase in the use of pneumothorax, pointed out that, as the indications for this type of therapy were extended, an ever larger proportion of unsatisfactory results was to be expected. In spite of the failures, however, the results of treatment were designated as "distinctly gratifying," and the statement was made that more than 70 per cent of the patients studied in the survey were still alive, and three-fourths of them able to work. "With due consideration of its very considerable limitations," the report concluded, "artificial pneumothorax appears to be undeniably one of our most valuable therapeutic measures in the treatment of pulmonary tuberculosis." With this conservative statement few, at the time, would have disagreed.

A coldly statistical analysis by Drolet (13) a few years later threw some grave doubts on the over-all success of the procedure, but an editorial (14) in the same number of the AMERICAN REVIEW OF TUBERCULOSIS, while granting that Mr. Drolet had served a useful purpose in "rocking the complacency" of the medical profession, pointed out what seemed to be oversights in his complicated analysis of data, and called attention to improvements in course in the techinques of collapse therapy, and still more radical surgery, which might be expected to change the picture entirely.

Our diligent and devoted fellow-workers in administrative positions in the antituberculosis campaign were as a rule less technically critical, since the majority of phthisiologists were with them. An example, which need not be documented, was a query by the executive director of a state tuberculosis association, who responded to a diffident approach for more money by the Director

of Medical Research as follows: "Do you really need it; isn't it true, now that we have mass x-ray surveys and pneumothorax, that we have all the weapons we need?"

In any event, the most optimistic physicians could only admit that, in spite of pneumothorax, a substantial number of tuberculous patients failed to make anything like the desired progress. More often than not, these treatment failures were attributed to unsatisfactory collapse, and many were the supplementary operations devised to take care of this hard core of disappointing cases. Improvement in many patients was so spectacular, on the other hand, as to convince all but the most critical of the general efficacy of the method; and the practice of setting up controlled rosters of like cases was not investigated sufficiently to learn if many of these spectacular cases might not have shown gratifying improvement without pneumothorax.

Emphasis was still on the failures, rather than on the successes. At the height of the fresh-air period, Robert Philip had spoken confidently of its general success, but admitted that "disappointments were frequent." The latter were attributed chiefly to failure of the patient to follow the rules. The failures of pneumothorax were credited during its last ten years of ascendancy to imperfection in the mechanics of the procedure and a host of resultant untoward complications. The hard core was now increasingly conspicuous because so much attention was focused upon it.

Chemotherapy

Streptomycin struck an entirely new note in the confidence of the medical profession in the treatment of tuberculosis. An assurance never felt before began to pervade the field. The discovery of the drug's toxicity and the emergence of bacterial resistance were set-backs, but these untoward effects were soon overcome by combination therapy with para-aminosalicylic acid and safer regimens. Resectional surgery at last became possible with the covering protection of the two drugs. Results were so much better than those obtained with pneumothorax and pneumoperitoneum that phthisiologists were wont to smile at the delusion they had been under when these operations were standard therapy. It scarcely seemed possible that they had been extolled as life-saving. It was a new experience to observe the clearing of roentgenographic shadows without the obscuring features of pneumothorax and thoracoplasty. The Therapy and Streptomycin committees of the American Trudeau Society (15) characterized the therapeutic effect upon well-established experimental tuberculosis in guinea pigs as unprecedented, and called streptomycin the first antibacterial drug proved definitely promising in the treatment of certain types of pulmonary and extrapulmonary tuberculosis in man.

The discovery of isoniazid seemed a case of the cup running over. To be sure, the initial statements were conservative, calling attention to dangers, known shortcomings, and all the uncertainties of not fully tried remedies. But the mature analyses of later years fulfilled the early optimistic hopes. In 1955 the Committee on Therapy of the American Trudeau Society (16) called anti-

microbial therapy the keystone in the medical management of tuberculosis. It noted that, thanks to antimicrobial therapy as well as other advances in technique, surgical mortality and morbidity rates had been reduced to very low figures. The recent abandonment of tuberculosis divisions as special entities in city, state, and federal departments of health is perhaps the most impressive indication of the current confidence in chemotherapy.

The old hard core has cropped up in every report, however. A seminar, in the program of the current meeting, on treatment failures in chemotherapy, after some attempt to define success and failure, resolved itself into a discussion of regimens of antimicrobial treatment. To me it was strongly reminiscent of the protracted discussions of treatment failures in the pneumothorax period, in which emphasis was laid, not on the character of the patient, but on a weird variety of procedures for securing a more effective collapse.

Reservations on the success of antimicrobial therapy have been greatest in the most severe forms of tuberculosis. It has been noted repeatedly that tuberculous meningitis, though once always fatal, has yielded progressively to advances in treatment with antimicrobial agents. In streptomycin days, it was said that therapeutic failures occurred in at least half of adult patients with tuberculous meningitis (17); in a later report (18) in the isoniazid era, it was noted that 90 per cent or more might be expected to survive. The hard core was still evident. But now, no one could say that chemotherapy was not more important than any other measure in treatment, for at one time all of the 90 per cent of surviving patients would have died. It was indeed fortunate for them that they acquired their tuberculous meningitis in the nineteen fifties rather than in the nineteen thirties. One is reminded of Allen Krause's remark in 1918, in an essay paying tribute to the advances of the day in tuberculosis therapy: "I know many men alive and highly productive today," he said, "who had the good fortune to become consumptive in the early nineteen hundreds rather than in the eighteen seventies." (19).

In each case therapy was unquestionably a factor in the good results. But no man stressed the other side of the coin more forcefully than Krause. I have already quoted his remark that not all tuberculosis is continuously progressive and that indeed only the rare cases are. The statement was written at a time when most persons did become infected. The resistance displayed by the population when so many were infected and did not die was more conspicuous than today, when such a high percentage of early cases are subjected to chemotherapy. Much attention was devoted to the resolution process by which infection, even advanced disease, was overcome. No clearer exposition of the facts has been written than that of J. Burns Amberson (20) in his early paper on "The Absorption of Pulmonary Deposits," which emphasized the natural tendency to heal, and a later editorial entitled "Has Tuberculosis Treatment been Effective?", which stressed the therapeutic value of rest alone.

What is most worth noting is the greater reliance on treatment now than has ever taken place before. A perfectly extraordinary concept has grown up of a man so permeated by a drug suppressing the growth of tubercle bacilli

that he is *ipso facto* a totally unsatisfactory culture medium for the organism's growth. Rest, which was the backbone of sanatorium treatment and even of its once major auxiliary, collapse therapy, was never envisioned as playing such a role. But the possibilities of streptomycin, isoniazid, the thiocarbanilides, and other drugs under study today are assessed in terms of the amount of dissolved drug that will prevent the growth of tubercle bacilli in a culture medium, or with intended closer approximation to the more exalted state of man, by measuring the concentration that will restrain their growth in the tissues of a mouse.

The remarkable fact is, and this is the belated point of the story, that some men do better than others when they attain such beneficial concentrations; and some do not do well at all. In other words, there must be individual factors that transcend even the best of therapy.

Factors in "Immunity"

The existence of such factors is generally conceded. Every now and then we are reminded of them forcefully, as, for example, in the case of the children in the Lübeck disaster, some of whom succumbed, while others survived; some with serious disease, and others with little progression of lesions, after inoculation with approximately (but not exactly (21)) the same dose of contaminated BCG vaccine. But of the nature of these factors we have only a smattering of knowledge. Some of them are certainly acquired. The very infection sets up in the host a train of altered responses inimical to its own progress. But some force exists in the host to make that possible. We designate such forces under broad titles like native and constitutional resistance or inherent immunity. Aside from these forces, however, there appear to be innumerable factors, applying more or less transiently, which may be of equal moment, and which for present purposes we can discuss in relation to our broadly conceived element of personal immunity.

Altogether aside from age, sex, and race, for which I shall not take time, certain physical attributes may be important. As far back as the time of Hippocrates some physical types of person were believed to be more resistant to tuberculosis than others. For centuries it was accepted that tall, thin men and women with light skin and blonde hair were more susceptible to the disease than shorter, squatter, darker persons. After the recognition of contagion, such concepts were scouted and finally scoffed at. Lately, however, two or three well-documented reports from large studies on military personnel, in which statistical control was as nearly rigid as possible, have borne out the old concept (22, 23). Why one type of body build should be more resistant than another, no modern student has had the temerity to say. The unexpressed thought seems to be that the characters named are genetically linked with other factors that are truly pertinent to native resistance. Some of these may now be considered.

Greatest attention has been concentrated on the body's hormones. Since these are normal constituents of the body, any unusual effects they have must be mediated through insufficiency or excess. Hints have come from the be-

havior of tuberculosis in the presence of known endocrine abnormality. It has been recognized for a long time that persons with insulin deficiency to the point of precipitation of diabetes mellitus have low resistance to tuberculosis. Conversely, it has long been held that persons with an excess of thyroid hormone, as manifested by the symptoms of hyperthyroidism, are little prone to the development of tuberculosis.

A great controversy has arisen over the effects of the steroid hormones of the adrenal glands. When cortisone was found efficacious in numerous ailments, it was, of course, tried in tuberculosis. The results seemed startlingly bad. Further research on experimental animals appeared to confirm the clinical observations. Removal of the factor of inflammation, a characteristic effect of cortisone, seemed to rob the body of some of its defenses. On the other hand, this suppressive effect on inflammation was not an unmixed detriment. In certain forms of tuberculosis, particularly meningitis, suppression of inflammatory exudation seems beneficial. So, in recent times, the concept of cortisone as a two-edged sword has grown up (24); it may help or hinder according to the type and location of the disease, and in any event, if used as a remedy, is to be so used only in association with antimicrobial therapy.

For our present purposes, it need be recognized only that cortisone does modify resistance and that therefore physiologic differences in the body's own production, which may occur as a result of a variety of stresses or strains, can be highly significant. Since for physiologic purposes we must have our own cortisone, and since under certain circumstances it may depress our resistance to tuberculosis, it seems obvious that a proper balance is essential; the person who has the physiologic capacity to maintain a favorable balance as far as tuberculosis is concerned has the edge when it comes to resistance to this disease. Many facts have been learned about cortisone in relation to tuberculosis, but not nearly enough to answer the questions that arise in clinical observation. When we add to that the fact that cortisone is only one of thirty or forty steroid hormones secreted by the adrenal gland or associated in its action, an overwhelming complexity of the problem is evident.

A review of physiologic characteristics bearing on resistance to tuberculosis would be incomplete without mention of mental attitudes. These are perhaps the least well defined of all such characteristics, but it seems generally believed that mental factors are important. In the last analysis, they may merely represent hormonal factors conceded to be significant. This is no place to debate that fundamental problem. But such diverse mental attitudes as anxiety, complacency, will power, determination, cooperativeness, hostility, care, and carelessness have been described many times as favoring or controlling the progress of tuberculosis in an infected person. Most of us believe they are important, although we have little idea how they act. To some they even seem to play as vital a role in human tuberculosis as the use or non-use of chemotherapy.

This brings me to an extraordinary factor in personal resistance that is concerned only in antimicrobial chemotherapy, viz., individual personal response to the presence of antimicrobial drugs in the system. Much evidence has ac-

cumulated in recent years to show that people vary in their capacity to inactivate isoniazid. The latter is by no means purely selective for tubercle bacilli. Body cells recognize it as a foreign toxic element and proceed to tie something to it, usually by the process of acetylation, that will render it inert as a cellular poison for them. Unfortunately, it seems to be at the same time rendered inert for the tubercle bacillus. Evidence has accumulated to indicate that the persons who do not put it out of the way rapidly show a better therapeutic response to the drug than those who do. If this proves to be true, this specialized physiologic attribute will be recognized as an important factor in resistance or susceptibility to tuberculosis under modern conditions.

We have discussed innate physiologic characters that bear on the problem. There are transient factors of quite similar significance. To some extent the state of nutrition is a constitutional character, but one that is easily modified. A relation between "good" nutrition and resistance to tuberculosis has always been accepted. Some people go so far as to say that there is a perfect state of nutrition that is incompatible with the progress of tuberculosis. While this is undoubtedly an exaggeration, much has been published recently to indicate that certain elements in the diet, particularly protein, vitamin A, and ascorbic acid, favor resistance. Starvation has always been supposed to predispose to tuberculosis. Lately, a remarkably deleterious effect of acute transient starvation, out of proportion to the long-term effect of chronic starvation, seems to have been demonstrated (25).

We have discussed the effect of concomitant disease. Diabetes and thyroid abnormalities have been mentioned. Alcoholism might have been mentioned as a disease or as a behavioral problem. An occupational disease, silicosis, has a recognized effect. In other diseases an effect is suspected, but is inconspicuous because of the gravity of the nontuberculous ailment. Leprosy is an example. Traditionally measles and whooping cough favor the progress of tuberculous infection. In mitral stenosis, vascular hypertension, chronic bronchitis, and asthma, the correlation with tuberculosis is low.

Concomitant diseases are among the many accidents that may affect the course of tuberculosis. Sometimes the effect of accident is more nearly obvious. Not rarely, tuberculosis develops at the site of an actual trauma. The old idea of a *locus minoris resistentiae* has not been abandoned. The main point is that there are especially bad times for adverse circumstances, such as an injury to the back or chest, the occurrence of measles, or overtreatment with cortisone.

In final analysis, the factors favoring or impeding the progress of tuberculosis in the body are presumably biochemical. Dubos (26) has listed many normally occurring products of metabolism that might restrain the growth of tubercle bacilli *in vitro* and might be expected to do so *in vivo* if present in excess of the normal concentration. The list includes such simple substances as lactic acid and acetone bodies, normally occurring amino acids, and a number of polyamines, as well as the more complex peptides, and still more complicated proteins. These he has grouped under the broad concept of biochemical determinants of disease. Some are concerned in nutrition and some in disordered

metabolism, while others are of accidental occurrence. The variety of combinations that might be imagined is almost infinite. It is not unrealistic at all to think that such substances, transiently or over long periods of time, by promoting or restraining the growth of tubercle bacilli, might tip the balance of power between host and parasite one way or the other.

In short it is evident that many personal factors, influencing what for present purposes I have very vaguely called immunity, can support or interfere with our modern antimicrobial and surgical therapy. Some of these, like nutrition, accident, and concomitant other diseases, may, in general, be readily controlled. Some, on the other hand, like the balance of those hormones that seem to be concerned in resistance to infection, are not readily susceptible to control. They are highly individualistic, and necessitate that individual consideration which has always been the heart of good medical care.

Finally, it is well to have in mind the revolutions we have seen in the therapy of tuberculosis. Past history suggests that the present is just one more era. We can be proud of its successes, but we have no reason to believe that it represents the last word.

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THE INFLUENCE OF FIBERGLAS®-PLASTIC DUST ON TUBERCULOSIS[1]

An Experimental Inhalation Study of Two Varieties of Dust: Histopathologic Observations

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Introduction

The close association between the inhalation of siliceous dusts and progressive tuberculosis is both a statistically impressive phenomenon (1–6) and a well-documented laboratory observation (7, 8). There is adequate proof of the capacity of crystalline-free silica to aggravate a tuberculous infection in both man and experimental animals. The propensities of combined silica in this respect are less well established. Unfortunately, out of this uncertainty has grown a widespread and firmly entrenched belief that all noncrystalline siliceous dusts are harmless. Many undoubtedly are. Other amorphous silicas and silicates have tuberculogenic capacities of variable significance. Nothing is known about the majority of these substances for the reason that the biologic actions of fewer than 10 per cent of the more than 500 known siliceous minerals have been explored.

The lack of information about the role of other types of dust in influencing the course of human or experimentally induced tuberculosis is even more disconcerting. Hopefully, most of these substances are relatively inert, and some even appear to impart resistance to tuberculous infections (9). More than six million industrial workers are exposed to nonsiliceous dusts in the United States alone. If tuberculosis were promoted by inhaled dusts of diverse kinds, there would be more definite positive correlation between occupations and selective prevalences of the disease than is at present on record.

The possibility remains that two or more seemingly inert substances in combination may modify the course of tuberculosis. The Fiberglas®-plastic which is the subject of this study presents such a problem. It is a conglomerate of glass fibers (about 15 per cent), polymerized polyester resin (about 35 to 60 per cent), and either calcium carbonate or calcium sulfate fillers (about 25 to 45 per cent). None of the component substances have clinically been proved to be tuberculogenic agents. The glass fibers, of course, are siliceous. No studies on the influence of inhaled glass fibers on tuberculosis have, so far, been undertaken, although particulate glass wool and glass cotton have been exonerated as serious pulmonary

[1] This study was sponsored by the Owens Corning Fiberglas Corporation, the Libbey-Owens-Ford Company, the Pittsburg Plate Glass Company (Fiber Division), the Molded Fiber Glass Body Company, and by the Office of Naval Research (Contract Nonr 1871(01)). The experimental phases of the study were completed at the Saranac Laboratory, Saranac Lake, New York.

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pathogens unless introduced in an overwhelming dosage (10, 11). Nothing conclusive is on record concerning the capacity of polyester resin plastics to influence pulmonary tuberculosis. There has been desultory support for the concept that various organic substances may facilitate the development of tuberculosis or aggravate its progression (12), but, on the whole, the issue remains in doubt. Calcium carbonate and calcium sulfate have generally been regarded as inert substances (13), but a recent study has indicated that inhaled calcium sulfate may transiently augment experimentally induced tuberculosis in guinea pigs (14). These conflicting observations, therefore, add interest to the study of the Fiberglas-plastic dust.

Materials and Method

The various steps involved in the manufacture of the somewhat complicated Fiberglas-plastic have been outlined elsewhere (15). The risk of occupational exposure appears to be greatest in the handling of the finished product. The calcium-carbonate-filled substance is, at present, popularly known as molded Fiberglas-plastic and is used chiefly in the manufacture of automobile bodies. The calcium-sulfate-filled product is best known as sheet Fiberglas-plastic, which is used extensively as structural partitions in buildings, as materials for furniture, et cetera.

In the conduct of the experiments which form the basis of this report, female guinea pigs of the Saranac Laboratory albino strain were used. These animals were all derived from a single pair and, through careful breeding over the past three decades, have developed a relatively high resistance to pulmonary infections other than tuberculosis. All of the animals were kept on a uniform standard vegetable diet throughout the course of the experiment.

The tuberculous infection with the R1Rv strain of human *Mycobacterium tuberculosis* was effected by means of the classic inhalation technique which has been fully described elsewhere (16). The experiments involving the calcium-sulfate- and calcium-carbonate-filled varieties of Fiberglas-plastic were initiated at an interval of ten months. In the first study with the calcium-sulfate-filled material the culture of R1Rv tubercle bacilli was going through a phase of reduced virulence for normal guinea pigs; but when the study with the calcium-carbonate-filled plastic was commenced, the stock culture had reverted to normal virulence. The reason for these fluctuations in the potency of the culture has never been found, but the phenomenon stresses the importance of controls for every study.

Except for their duration, the exposures were conducted in a directly comparable manner in 8 by 8 by 8 ft. chambers, the dust being disseminated by means of a hopper-and-paddle mechanism. In the study with calcium-sulfate-filled plastic (*Experiment 1245*), the average level of exposure was 399 million particles per cubic foot and the monthly average exposure over a period of ten months ranged from 18 to 775 million particles per cubic foot. During the study with the calcium-carbonate-filled dust (*Experiment 1259*), which continued for twenty-four months, the average particle count per cubic foot was 338 million with a range of 52 to 792 million.

Control Studies

Guinea pigs not exposed to the Fiberglas-plastic dust, but infected with R1Rv tubercle bacilli, served as controls. By comparison with the established effects on guinea pigs (7, 8, 14, 16), the tuberculous responses in these control groups may be graded as *minimal* in the case of *Experiment 1245* (tables 1 and 2) and *average* in the case of *Experiment 1259*. The self-limiting character of the lesions and the insignificant extrapulmonary dissemination of the infection require special emphasis. Typical lesions are illustrated in figure 1.

TABLE 1

THE INFLUENCE OF INHALED FIBERGLAS-PLASTIC DUST ON THE COURSE OF EXPERIMENTALLY-INDUCED PULMONARY TUBERCULOSIS

Control Study: No Dust Exposure

Gross Observations

Female guinea pigs were infected by inhalation with R1Rv tubercle bacilli and killed at regular intervals; no spontaneous death occurred.

Animal Number	Time Lapse After Infection	Lungs			Lymph Nodes				Splenomegaly
		Tuberculin Reaction	Subpleural Tubercles		Tracheobronchial		Hepatic-Portal		
			Average Number	Type	Enlargement	Induration	Enlargement	Induration	
Experiment 1245: Control to Groups Exposed to Calcium-Sulfate-filled Fiberglas-Plastic Dust									
	months								
112, 113	2	+++	4	D	++	++	+	+	
114, 115	4	+++	6	H	++++	++	++	++	
116, 117, 118	6	+++*	5	H	++	++	+	+	
119, 120	8	+++	3	H	++	++	x		
140, 142, 143, 144	10	+++	2	H	++	+			
Experiment 1259: Control to Groups Exposed to Calcium-Carbonate-filled Fiberglas-Plastic Dust									
112, 113	2	++++	17	D	++++	++	+++	++	+
114, 115	4	++++	9	Cs	+++	++	++	++	+
116, 117	6	+++	10	D	+++	++	++	++	+
118, 119	8	++++	10	H	++	++	+		+
120, 121	10	++++	6	H	++	++	+	+	+
122, 123	12	++++	7	H, D†	++	+	+++	++	+
124, 125	14	++++	8	H-Cs	+	++	+		+
126, 127	15	++++	8	H-Ca	++	+	+		x
128, 129	16	++++	3	H	+	++	x		
130, 131	18	++++	2	H	++		x		+
132, 133	21	++++	4	Cs, H	+	++	x	x	
134, 135	24	++++	2	H	++	++	+		

Symbols: + slight reaction, ++ moderate reaction, +++ marked reaction, ++++ extreme reaction, H healing, Ca calcification, Cs caseation, D developing tubercle, x present in one animal only.

* The tuberculin reaction was negative in animal 1245-117.

† There was a tendency for tubercles to spread locally in animal 1259-123; healing was evident in 1259-122.

Simultaneous-Phase Study

In each experiment, 25 guinea pigs were infected with R1Rv tubercule bacilli and then placed immediately in the dust room where they remained until death. One animal only from each group died from intercurrent pulmonary infection, apparently unrelated to the tuberculous process or the pneumoconiotic response.

TABLE 2

THE INFLUENCE OF INHALED FIBERGLAS-PLASTIC DUST ON THE COURSE OF EXPERIMENTALLY-INDUCED PULMONARY TUBERCULOSIS

Control Study: No Dust Exposure

Pulmonary Histopathology

Female guinea pigs were infected by inhalation with R1Rv tubercle bacilli and killed at regular intervals; no spontaneous deaths occurred.

Animal Number	Time Lapse After Infection	Lymphoid Hyperplasia	Focal Mural Infiltration	Focal Hyperemia	Tubercles						Peribronchial Reaction
					Epithelioid Cells	Caseation	Encapsulation	Fibrosis	Calcification	Resolution	
Experiment 1245: Control to Groups Exposed to Calcium-Sulfate-filled Fiberglas-Plastic Dust											
	months										
112, 113	2	x	x		+++						C++
114, 115	4	x	xx		++	++		+		+	C+
116, 117, 118	6				++					+++	
119, 120	8		x		+					+++	
140, 142, 143, 144	10				+			+		++	
Experiment 1259: Control to Groups Exposed to Calcium-Carbonate-filled Fiberglas-Plastic Dust											
112, 113	2	++++	xx		+++	+++					C++
114, 115	4	+			+++	+++	+	++	++	++	C+
116, 117	6	x		xx	+++	++	++	+		+++	
118, 119	8	+	+		++	+			xx	+++	
120, 121	10				+	xx	xx	xx	xxx	+++	
122, 123	12	x	x		++	xx	xx	xx	x	x	F++
124, 125*	14				+			xx	+++	xxx	
126, 127	15		xx	xx	+			++	++	xx	F+
128, 129	16		x	xxx	+				xx	x	
130, 131	18			++	+			+		++	
132, 133	21				+	xx		xx	xx	xx	
134, 135	24			+++						+++	

Symbols: + slight reaction, ++ moderate reaction, +++ marked reaction, ++++ extreme reaction, C cellular reaction, F fibrosis, x–xxx present in one animal only.

* A moderate degree of emphysema was present.

RESULTS

The two inquiries resulted in vividly contrasting responses. The calcium-sulfate-filled Fiberglas-plastic dust augmented the tuberculous infection only to a slight degree. Despite continued dust exposure, healing commenced early with little fibrosis, encapsulation, or calcification, and occurred principally through regression of cellular aggregations and phagocytic resorption of necrotic material. In the case of the extrapulmonary organs, resolution occurred equally promptly and to the full state of completion seen in the control group.

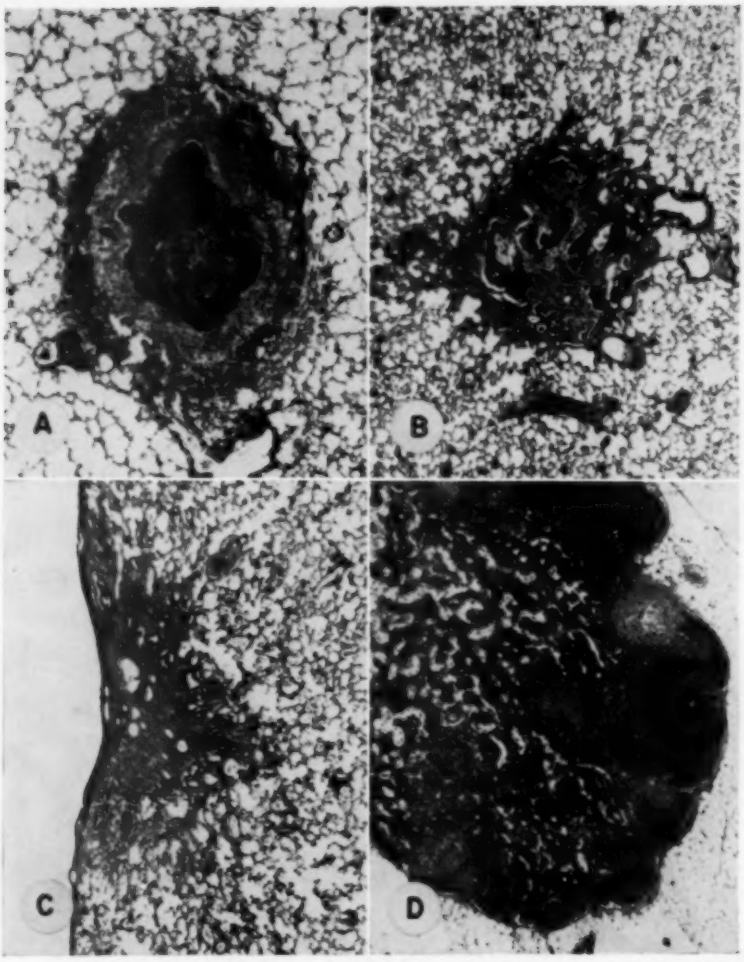

FIG. 1. Control guinea pigs infected by inhalation with R1Rv tubercle bacilli. No dust exposure. (Hematoxylin and eosin)

A. 4 months: Shows a typical R1-induced tubercle with abundant central caseation but with incipient encapsulation. (× 35)

B. 12 months: The tubercle has healed almost completely through partial resorption of the caseous center and replacement by fibrous connective tissue and calcium. (× 35)

C. 15 months: Residual depressed subpleural scar representing a healed tubercle. (× 35)

D. 2 months: Typical fibrocellular tubercles in the tracheobronchial lymph nodes. (× 10)

The responses achieved during the simultaneous exposure of infected guinea pigs to the calcium-carbonate-filled Fiberglas-plastic contrast sharply with both

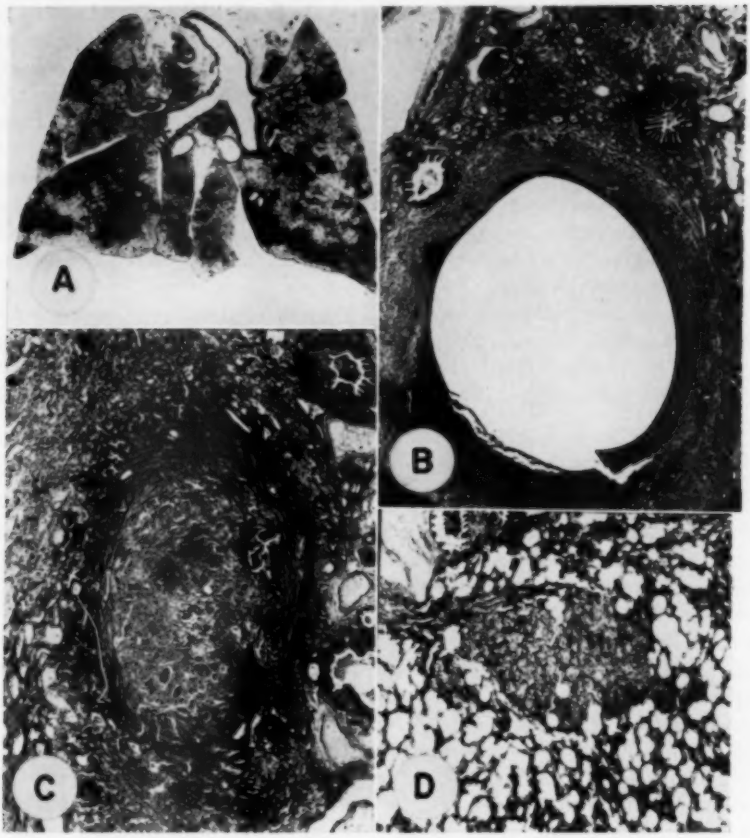

FIG. 2. Simultaneous phase study: Guinea pigs infected by inhalation of R1Rv tubercle bacilli and immediately thereafter exposed to Fiberglas-plastic dust (calcium-carbonate-filled). (Hematoxylin and eosin)

A. 4 months: The lesions demonstrate spreading of the tuberculous process in some animals. (× 1)

B. 15 months: Typical cavitary tuberculous lesion. (× 35)

C. 15 months: Previously spread lesion healing through encapsulation and interstitial fibrosis. (× 35)

D. 24 months: Individual macrophage cluster which is smaller than lesions of equal age in the uninfected control guinea pigs. (× 35)

the foregoing results and the reactions observed in the control group. In a large proportion of the animals, there was significant spread of the tuberculous process during the first year of exposure to the dust. Not only were individual tuber-

cles more numerous and larger than those in the lungs of the control guinea pigs but, in most instances, they also displayed marginal confluence (figure 2*A*). Thus, relatively extensive portions of the lungs became involved. This enhanced reaction was, however, limited to the pulmonary parenchyma, the lymph nodes displaying virtually no increased tuberculous granulomatosis. Caseation, fibrosis encapsulation, interstitial fibrosis, calcification, and excavation of lesions occurred throughout the course of the dust exposure. The cavities which formed (figure 2*B*) generally were the result of extrusion of liquefied caseous contents and with limited secondary erosion. Cavitation was not the rule. Many lesions healed by concentric fibrosis after resorption of the necrotic contents of conglomerate and expanded lesions.

It is of particular interest to note that the enhanced tuberculous reaction did not simultaneously aggravate the pneumoconiotic response (figure 2*D*). On the contrary, the peribronchial and parabronchial collections of koniophore macrophages were decidedly less extensive than were those in uninfected control animals (15).

Reactivation Study

The underlying principle in this type of experiment involved delay of the dust phase long enough to be able to prove the influence of such exposure on the nascent, declining, and arrested tuberculous infection. In each experiment, 26 guinea pigs were employed. In view of the manifestly abortive character of the reaction in the case of *Experiment 1245*, dust exposures were discontinued after ten months from the date of infection, and the remaining animals were discarded. All 26 animals of *Experiment 1259* were sacrificed as originally planned, and dust exposure was continued for twelve months. None of the guinea pigs died prematurely.

Although the dust exposure, which followed within two months from the date of infection, mildly but transiently reactivated the tuberculous infection, the calcium-sulfate-filled Fiberglas-plastic dust actually accelerated the healing of the tuberculous process when the dust exposures were continued after four and six months, respectively. This was evident both on inspection of the guinea pigs and comparison of the gross features of the lungs and lymph nodes with those of the unexposed infected controls sacrificed at the same time. Microscopic examination further emphasized these limited responses. Appreciable caseation and fibrosis were observed in 2 animals only, and the majority of the tubercles consisted of epithelioid cell clusters. Resolution commenced early and was complete in most instances by the end of the ten months following the infection. The reactions in the tracheobronchial lymph nodes were similarly limited, and there was no extrathoracic dissemination of the disease.

In the group of guinea pigs exposed to the calcium-carbonate-filled Fiberglas-plastic dust, the tuberculous response was transiently enhanced. Not only were the lesions more numerous in the guinea pigs which were exposed to the dust after two months, but individual tubercles were larger, marginal confluence occurred, and there was moderately extensive central caseation with abortive

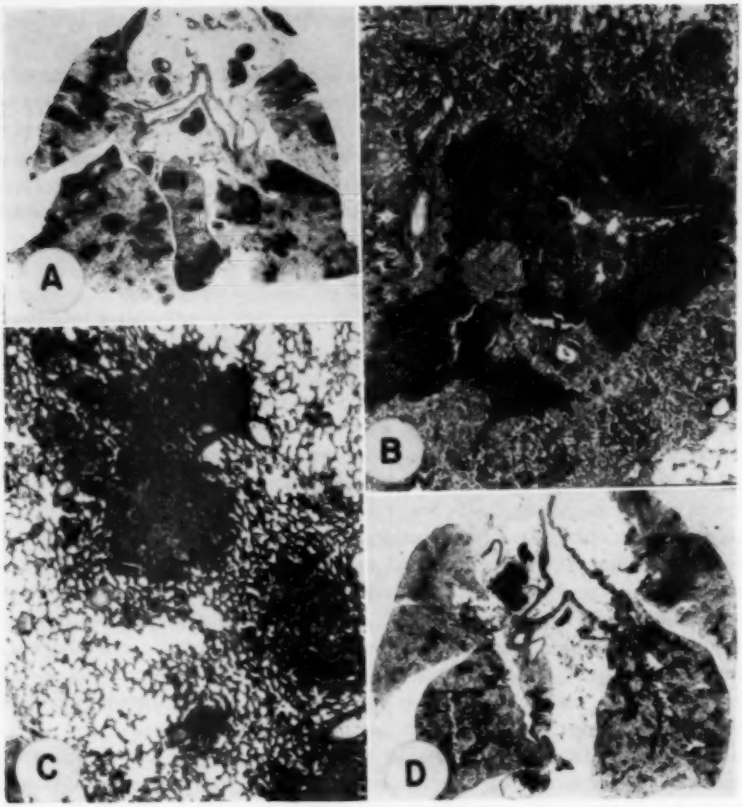

FIG. 3. Reactivation phase study: Guinea pigs infected by inhalation with R1Rv tubercle bacilli. After periods varying from 2 to 6 months, the animals were exposed to Fiberglas-plastic dust (calcium-carbonate-filled). (Hematoxylin and eosin)

A. Infection 14 months plus dust exposure 12 months. Individual tubercles are in a proliferative state, but no lymph node involvement is present. (× 1)

B. Infection 14 months plus dust exposure 12 months. Detail of tubercles shown in *A* revealing caseating center and incipient excavation. (× 35)

C. Infection 16 months plus dust exposure 12 months. Previously reactivated tubercles have undergone regression without fibrosis or calcification. (× 35)

D. Infection 18 months plus dust exposure 12 months. The tuberculous process has been mildly reactivated. The majority of the lesions are pneumoconiotic foci and these are less numerous and smaller than in the uninfected guinea pigs. (× 1)

cavitation (figures 3 *A* and *B*). These tubercles healed relatively rapidly, necrotic material became resorbed, and there was slight residual fibrosis in a number of cases. The lymph nodes were involved to a slight or moderate degree only. Apart from slight centrilobular liver-cell atrophy and slight Malphigian corpuscle

hyperplasia in the spleen, there was no significant extrapulmonary reaction to the infection and dust exposure.

In guinea pigs which were placed in the dust room at later stages, the tuberculous reactions were correspondingly reduced. Although mild reactivation still occurred in these animals, the process was limited to epithelioid cell hyperplasia which subsequently resolved (figure 3*C*). The pneumoconiotic process was also considerably inhibited in these guinea pigs (figure 3*D*). Not only were the clusters of dust-filled multinucleated giant cells less numerous than in uninfected guinea pigs, but individual lesions were smaller, and some parts of the lungs remained unaffected.

The extrapulmonary organs were involved to an even lesser extent than in the group of guinea pigs placed in the dust room two months after infection.

Discussion

Several conundrums were solved by the present study. First, it was proved that, although the two types of dust contain silicon dioxide, polymerized polyester resin, and either calcium sulfate or calcium carbonate, the combined presence of these substances did not seriously enhance the granulomatous process induced in guinea pigs by R1Rv tubercle bacilli. Second, it was shown that the tuberculous response was not proportionate to the degree or duration of the dust exposure. Healing of previously spreading tubercles took place despite continued dust exposure. This tolerance for the tuberculous infection manifested itself even though it has been established (15, 17) that the prolongation of the Fiberglas-plastic dust exposure progressively increased the size of the pneumoconiotic lesions. Third, it was further demonstrated that mere enhancement of the level of dust exposure was not the prime factor in determining the severity of the tuberculous process. The dust count was higher in the study with the calcium-sulfate-filled plastic dust, and yet the tuberculous reaction was decisively less marked in these animals as compared with the reaction in guinea pigs which inhaled the calcium-carbonate-filled Fiberglas-plastic dust.

A fourth point of interest concerns the immediacy of the tuberculous response. Clearly, in this instance it was the presence of the inhaled and retained dust in the lungs of the guinea pigs, and not the prior establishment of pneumoconiotic lesions, which acted as the tuberculogenic factor. As the specific pneumoconiotic lesions evolved, the tuberculous process decreased. This feature, coupled with the observation that the koniophore clusters (which characterize the response to the inhaled Fiberglas-plastic dust (15)) were reduced in size and number by the associated or prior presence of the tuberculous infection, may indicate that the epithelioid cells and the phagocytic macrophages which form integral components of the specific responses may have a common origin. The biologic competition for these cells by the bacteria and the dust particles may limit the tubercle formation whenever the pneumoconiotic lesions become too readily established, or the early pre-emption of these cells in tubercles may militate against the maturation of dust-produced lesions. The tuberculosis produced by R1 is usually mildly fibrogenic. Enhanced pulmonary fibrosis could a priori,

therefore, have been expected as a result of the transient spread of the tuberculous process. This did not occur.

It was shown that Fiberglas-plastic dust was not fibrogenic for guinea pig lungs (15), and it now seems possible that this substance may actually resist the deposition of collagen. Such a property would naturally facilitate the resolution of the enhanced tuberculous process for, in classic tuberculosilicosis, the dense scar tissue helps to prolong the infectious component. The slight alveolar capillary hyperemia induced by the plastic dust may further have facilitated recovery from the tuberculosis. In classic tuberculosilicosis, there is marked local ischemia which apparently contributes significantly in retarding the healing process (18).

The sharp difference in the results obtained with the two types of dust may have either of two explanations. Thus, it is possible that calcium sulfate may be less tuberculogenic than calcium carbonate. One prior study (14) revealed that calcium sulfate itself is able to enhance tuberculous infection mildly and transiently. Calcium carbonate may have similar properties, as Gardner (19) demonstrated many years ago that inhaled marble dust may cause transient pulmonary spreads in tuberculous animals. However, these earlier experiments are not directly comparable with those conducted with calcium sulfate, and the results of the marble study were further vitiated by intercurrent epizootics. It is not yet known, therefore, whether calcium sulfate is more or less tuberculogenic than calcium carbonate. The outcome of the present inquiry rather suggests the latter possibility. However, the fact that the R1 infection was going through a phase of reduced virulence during *Experiment 1245* and had recovered its normal properties during *Experiment 1259* further tempers the inferences which may be drawn from these contrasting results. It is possible that the virulence of the R1 bacillus may periodically be reduced to a subliminal level for the less vigorously tuberculogenic dusts. In the present instance, the reduced virulence of the R1 bacillus during the experiment with the calcium-sulfate-filled Fiberglas-plastic did not decrease the tuberculosilicotic responses which were obtained in infected guinea pigs concurrently exposed to quartz dust in another experiment.

Summary

The results of experiments probing the influence of two varieties of Fiberglas®-reinforced polyester resin on the course of experimentally induced pulmonary tuberculosis in 113 guinea pigs are reviewed. Both inhaled Fiberglas-plastic dusts caused limited transient augmentation of the R1 tuberculous infection. The tuberculous infection was more vigorous and of greater duration in the animals exposed to the Fiberglas-plastic dust with a calcium carbonate filler than in the guinea pigs exposed to Fiberglas-plastic dust containing calcium sulfate as a filler.

Sumario

El Influjo del Polvo de "Fiberglas" Plástico sobre la Tuberculosis

Estúdianse aquí los resultados de experimentos relativos al influjo de dos variedades de resina poliestérica de "Fiberglas®" reforzado sobre la evolucion de la tuberculosis

pulmonar inducida experimentalmente en 113 cobayos. Ambos polvos de "Fiberglas" plástico, al ser inhalados, provocaron limitado aumento pasajero de la infeccion tuberculosa por R1. La infeccion tuberculosa fué mas potente y duradera en los animales expuestos al polvo de "Fiberglas" plástico que contenia un complemento de carbonato de calcio que en los expuestos al polvo de "Fiberglas" plástico que contenía sulfato de calcio como complemento.

Resume

L'influence de la poussière de matière plastique Fiberglas sur la tuberculose

Analyse des résultats de recherches expérimentales sur l'influence de deux variétés de résine polyester renforcée Fiberglas® sur l'évolution de la tuberculose provoquée chez 113 cobayes. L'inhalation de poussières de ces deux types de Fiberglas a produit une augmentation transitoire de l'infection tuberculeuse R1. L'infection tuberculeuse était plus intense et plus durable chez les animaux exposés à la poussière du Fiberglas contenant du carbonate de calcium que chez les cobayes exposés à la poussière du Fiberglas contenant du sulfate de calcium.

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SILICOTUBERCULOSIS[1]

Results of Medical and Combined Medical-Surgical Therapy

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INTRODUCTION

Although the literature on the results of treatment of pulmonary tuberculosis is voluminous, only relatively few papers have reported the results of therapy of silicotuberculosis. The paucity of this literature plus the known increased incidence of pulmonary tuberculosis in silicosis, due either to a heightened susceptibility to this form of pneumoconiosis (1) or to a deleterious effect of the silicotic lesion on pre-existing disease (2), should make the subject of this paper interesting. With this hospital situated in a hard-coal mining region, where coal is extracted from silica-bearing rock, an exceptional opportunity was afforded the writers to treat a number of miners who had silicotuberculosis.

It is the primary purpose of this paper to report the roentgenographic and bacteriologic results of therapy in a small group of silicotic patients with tuberculosis, all with the diagnosis of silicosis made by occupational history and roentgenographic examination, and of phthisis by bacteriologic examination. As a corollary, the secondary purpose is to indicate the advisability of treating silicotuberculosis at its inception, as manifested by beginning conglomeration and a positive tuberculin test. All patients were treated with antituberculous drugs, while a small number of them were treated by various surgical chest procedures in addition to the drugs. Since this was initial chemotherapy for all patients, it was presumed that, at the onset of therapy, they were infected with tubercle bacilli susceptible to the antituberculous agents.

A few words or more would seem apropos on the interrelation of silicosis, coal-workers' or coal-miners' pneumoconiosis, and anthracosilicosis, upon which tuberculosis was superimposed in the patients of the present report.

Silicosis may be defined as a pneumoconiosis due to the deposition of inhaled silica dust alone; and coal-workers' pneumoconiosis, as one probably due to the deposition of coal dust alone. On the other hand, anthracosilicosis may be similarly defined as the result of the dusts of both silica and coal. It is known that coal dust itself, as well as silica, is injurious to the lungs; each is capable of producing a picture of generalized obstructive emphysema (1). With silica dust, the emphysema is the result of reactive fibrosis, while with coal dust it results from the obstruction of small bronchioles due to dust deposition (3). In anthracosilicosis, owing to the inhalation of both dusts, the pathologic changes apparently develop more rapidly and are more severe. Furthermore, in all three pneumoconioses, the likelihood of the development of emphysema is enhanced

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TABLE 1

DISTRIBUTION BY AGE OF 25 PATIENTS WITH SILICOTUBERCULOSIS AT THE BEGINNING OF CHEMOTHERAPY

Age of Patients	Employment in Mines	Number of Patients
years	*average number of years*	
30–39	11*	1
40–49	14	3
50–59	29	9
60–69	30	10
70–79	30*	1
80–89	6*	1
Total.....		25

* These figures represent the actual number of years of employment in the mines.

by the appearance of conglomerate disease. As silica is a common etiologic factor of both silicosis and anthracosilicosis, their pathologic features being similar, and as both produce similar chest roentgenographic patterns, anthracosilicosis may be regarded as a variant of silicosis.

MATERIAL AND METHODS

The patients of the present study were hard-coal miners. All were admitted to this hospital between September 10, 1952 (when a 38-bed tuberculosis section was activated), and December 1, 1956, and had bacteriologic confirmation of the diagnosis of pulmonary tuberculosis in the form of several sputum specimens positive for tubercle bacilli on microscopy and/or culture. All had roentgenographic evidence of silicotuberculosis; had had no previous course of chemotherapy; and were treated continuously with antituberculous drugs for at least a six-month period in this hospital. Twenty-five patients participated in this study and all but one satisfied the criteria; in the one exception, the chemotherapy had been interrupted for a relatively short period of time. All of these patients were white males.

The age distribution of the patients and the number of years they had spent in the hard-coal mines are shown in table 1. Nineteen of the 25 patients were in the age groups fifty to fifty-nine and sixty to sixty-nine years, with an average period of approximately thirty years' employment in the mines.

The chemotherapy regimens followed in the patients consisted of either a combination of two of the following three drugs or of all three drugs: streptomycin, sodium salt of para-aminosalicylic acid (PAS), and isoniazid. Most of the patients received streptomycin and isoniazid; relatively few were treated with any other combination or with all three drugs. Streptomycin was given by the intramuscular route, usually in a dosage of 1 gm. twice weekly; however, 1 gm. was administered daily to patients who were either acutely ill or in the immediate preoperative and postoperative periods. Para-aminosalicylic acid was given orally in a daily dosage of 12 gm. divided into three doses. Isoniazid was also administered orally in a daily dosage of 300 mg. divided into three doses. In the majority of patients the chemotherapy was started in this hospital, but in a few it was begun either at home or in another institution prior to admission here. In the latter group, chest roentgenograms and the results of bacteriologic examinations done in the pretreatment stage were obtained. Patients discharged from the hospital were referred to community health agencies for continuation of observation and chemotherapy. The course of these

patients was followed through readmission to the hospital, outpatient examination, or reports and chest roentgenograms received from the community health agencies.

While all patients received chemotherapy, 6 of the 25 were treated with both drugs and various types of thoracic surgery; chemotherapy was continued after completion of the surgical procedures. In addition to drug and surgical therapy, 2 patients were also treated with pneumoperitoneum. The procedure was discontinued in both instances because it added little to the chemotherapeutic effect.

As a chest surgeon was not available at this hospital initially, 3 patients were transferred to the Veterans Administration Hospital, East Orange, New Jersey, for surgery. Several months after the operation, these patients were returned to this hospital for continuation of their care. Later, when a chest surgeon became available here, surgical procedures in the other 3 patients were carried out at this institution.

Pulmonary function studies of a ventilatory nature were performed on almost all patients, especially those who were considered candidates for surgery.

While the patients were hospitalized, the results of therapy were followed by chest roentgenograms obtained every two months and by bacteriologic examinations performed once monthly. After their discharge, the follow-up observation proceeded in the manner mentioned above. The therapeutic efficacy of the medical and combined medical and surgical regimens was based on the criteria of closure or eradication of cavity proved by planigraphy, roentgenographic improvement other than cavity closure, and reversal of infectiousness. Conversely, inefficacy of therapy was based on the criteria of roentgenographic deterioration and bacteriologic relapse. Reversal of infectiousness was said to have occurred when sputum smears and cultures were found to be negative for tubercle bacilli for a period of at least three consecutive months, and bacteriologic relapse occurred when the sputum became positive for tubercle bacilli on microscopy or culture after reversal of infectiousness.

Studies of the susceptibility of the tubercle bacilli to streptomycin, PAS, and isoniazid were too few to be of significant value for incorporation in this paper.

Observations

Roentgenographic features: The frequency with which various types of roentgenographic manifestations of tuberculosis were encountered among the 25 patients is indicated in table 2. As it seems reasonable to assume that, in the presence of tubercle bacilli in the sputum, all conglomerate lesions or infiltrates are tuberculous, they have been classified as such. Twenty-one of the 25 patients had cavitary disease: 16 with single cavity and 5 with multiple cavities. There

TABLE 2

Distribution by Roentgenographic Features of the Chest of 25 Patients with Silicotuberculosis at the Beginning of Chemotherapy

Roentgenographic Features	Number of Cases
Single large conglomerate mass	3
Multiple large conglomerate masses	3
Single cavity	16
Multiple cavities	5
No cavity	4
Small conglomerate lesions	12
Pleural effusion	2
Pericarditis (enlarged cardiac shadow)	1

were only 4 cases in which cavitary disease was absent. Of these, 3 patients had large bilateral conglomerate masses while the fourth had only a relatively small conglomerate lesion.

There were several instances of active extrapulmonary tuberculosis. Two patients had pleural effusions considered to be of tuberculous origin. In one patient the fluid, positive for tubercle bacilli on culture, receded completely soon after the institution of chemotherapy. In the other, a thoracentesis was not done, and the fluid also disappeared within a short time after the start of chemotherapy. As noted in table 2, one patient had pericarditis, which was considered tuberculous in view of the presence of silicotuberculosis; the diagnosis of pericarditis itself was based on roentgenographic, electrocardiographic, and clinical signs. The chemotherapy for this patient, together with salt restriction and the administration of mercurial diuretics, resulted in the disappearance of the symptoms and signs of pericardial disease. Only one patient showed active tuberculous disease outside the chest cavity. This was the patient with pericarditis who had two tuberculous sinuses in the anterior chest wall which healed as a result of chemotherapy.

Results of chemotherapy: The results after chemotherapy for six months and after chemotherapy for an average period of twenty months are tabulated in table 3. In the group that received therapy for an average period of twenty months, only those patients were included who had been treated for at least nine months. Since 3 patients did not meet this specification, only 22 patients were in this group as contrasted with the original 25. It may be seen that there was a slight trend toward roentgenographic improvement with continuation of chemotherapy after the six-month period. Eleven (44 per cent) of the patients in the six-month group showed such improvement as compared with 12 (54 per cent) in the twenty-month group. This improvement was manifested chiefly by regression of small conglomerate lesions and decrease in size of cavity; in only one instance was there regressive change in a large conglomerate mass. As may be seen, there was no progressive trend toward cavity closure. There were only 3 cases of

TABLE 3

RESULTS OF CHEMOTHERAPY ALONE IN CASES OF SILICOTUBERCULOSIS

Months After Start of Therapy	6	Range: 9–48 Average: 20
Number of cases	25	22
Number of cases of cavitary disease	21	20
Roentgenographic improvement	11 (44%)	12 (54%)
Cavity closure	3 (14%)	3 (15%)
"Filled-negative" cavity	0	3 (15%)
"Open-negative" cavity	1 (5%)	0
Reversal of infectiousness	5* (20%)	6 (27%)
Roentgenographic deterioration	1 (4%)	10 (46%)
Return of infectiousness	0	1 (5%)
Death	0	7 (32%)

* One reversal of infectiousness was associated with a small conglomerate lesion.

closure of a single cavity, and those patients in the twenty-month group were the same as the 3 in the six-month group. There was no instance of closure of multiple cavities.

Roentgenographic deterioration became increasingly manifest with the continuation of chemotherapy. Only one patient showed such deterioration at the end of six months, contrasted with 10 (46 per cent) of the patients in the twenty-month group. There were 15 patients treated for at least twelve months; the results of therapy in this group, which are not shown in table 3, already showed a trend toward roentgenographic deterioration.

There was a progressive trend toward reversal of infectiousness with continuation of therapy. Five patients showed conversion at the end of six months of therapy. Three "conversions" were the result of closure of a single cavity; the fourth was in a patient who still showed a cavity, the so-called "open-negative" cavity; and the fifth was in the patient who demonstrated only a relatively small infiltration. In the twenty-month group, there were 6 reversals of infectiousness. These 6 included the afore-mentioned 3 patients with closed cavities and 3 additional cases, all the result of filling of cavities. The patient with the "open-negative" cavity in the six-month group was not a member of the twenty-month group since he had not received chemotherapy for nine months.

There was one instance of bacteriologic relapse in the twenty-month group which was the reason for only 6 and not 7 reversals of infectiousness in this group. This occurred in the patient with the small conglomerate lesion who developed a cavity despite continuation of chemotherapy after the six-month period.

There were no deaths in the six-month group, but there were 7 in the twenty-month group. At the time of death, 5 patients had infectious sputum, 3 showing deterioration roentgenographically just prior to death; the other 2 had noninfectious sputum and closed cavities. All 5 patients had heart disease, which was either the major cause or a contributory cause of death. Three of the 5 patients had developed heart failure secondary to the pulmonary disease; one had manifested failure on the basis of arteriosclerotic heart disease; while the fifth patient had suffered an acute myocardial infarction several weeks before his death, which occurred suddenly. Only 2 of these 5 patients, both with cavitary disease, were examined at autopsy. One was a patient with pulmonary heart disease in failure while the other was the patient with arteriosclerotic heart disease in failure. Post-mortem examinations confirmed the diagnoses, each showing the cardiac disease, silicosis, and tuberculous cavity.

The other 2 deaths occurred in patients who had had reversal of infectiousness due to closure of a single cavity, and who had remained noninfectious to the time of death. One patient died of adenocarcinoma of the lung with extensive metastatic disease. The post-mortem examination confirmed this diagnosis, the lungs also showing evidence of silicosis but not of cavitary disease. The second patient died of cor pulmonale in failure; no autopsy was done.

One of the patients with a filled cavity is the victim of cor pulmonale, with manifestations of failure in abeyance, on therapy with a low-sodium diet, digi-

talis, and occasional injections of mercurial diuretics. It should be noted that, of the original 25 patients, 5 (20 per cent) had developed cor pulmonale with failure.

Another patient with a filled cavity is eighty-four years of age. He has arteriosclerotic heart disease with manifestations of failure controlled by the usual cardiac regimen.

Results of combined therapy: Of the 25 patients comprising this study, there were 17 who had severe impairment of pulmonary ventilation as the result of extensive tuberculosis, silicosis, and emphysema. In the remaining 8, pulmonary function was considered adequate, and 7 of these underwent surgery; one patient did not require operation as the pulmonary disease became clinically inactive. The details with regard to 6 patients are given in the case reports. The seventh patient, who had a large cavity in the right upper lobe and apparently satisfactory pulmonary function, had a thoracotomy, but before the contemplated resection of the right upper lobe was started, he developed cyanosis and hypotension. Upon termination of the operation when these signs occurred, the patient recovered rather quickly. Several months later, he suffered a myocardial infarct and died suddenly, as mentioned previously. It was believed that the chest surgery and the myocardial infarct had no cause-and-effect relationship. Infectious just prior to surgery, the 6 patients presented in the case reports had unilateral cavitary disease. Preoperatively, they received courses of chemotherapy ranging from nine to forty-eight months. The reasons for the long delay in operation on several of the patients are given.

Case Reports

Case 1: The patient was a white male who had been employed in the hard-coal mines for thirty-one years. The preoperative pulmonary function studies limited to ventilation were satisfactory; bronchospirometry showed that the right lung, despite the cavitary disease in it, performed approximately 55 per cent of the ventilation. He received preoperative chemotherapy for about twelve months and pneumoperitoneum for approximately three months. On November 24, 1954, when the patient was fifty-six years of age, a right upper lobectomy to remove the large cavity and a small space-filling thoracoplasty were performed. His postoperative course was uneventful, and he received chemotherapy for one year postoperatively.

The patient was last seen on May 1, 1957, about seventeen months after the completion of chemotherapy, or twenty-nine months after surgery. Bacteriologic examinations for tubercle bacilli since the surgery had all been negative. Material taken from the cavity in the resected lobe was positive on microscopy and culture for tubercle bacilli.

Case 2: The patient was a white male who had been employed in the hard-coal mines for approximately twelve years. He had a course of preoperative chemotherapy for approximately forty-eight months, interrupted for a short period late during the course. The therapy was of this long duration because various hospitals did not consider it advisable to operate on him, apparently because of the silicosis. Presurgical pulmonary function studies showed moderate impairment of ventilation, obstructive in type. Bronchospirometry, also prior to surgery, showed the right lung to be performing approximately 30 per cent

of the ventilation. The preoperative chest roentgenogram showed extensive tuberculous disease, particularly in the right upper lobe, which contained a cavity. On May 15, 1955, when the patient was forty-four years of age, a right pneumonectomy was performed, and on June 22, 1955, it was followed by an extensive space-filling thoracoplasty. Except for the development of a bronchopleural fistula after the resection, the postoperative course was not remarkable. After the thoracoplasty the patient received chemotherapy for eighteen months.

The patient was last seen on March 12, 1957, about twenty-two months after the pneumonectomy, or about three months after completion of chemotherapy; he has had noninfectious sputum ever since the resectional surgery. The resected right lung showed extensive silicotuberculosis with only a small cavity in the right upper lobe. Microscopy and culture of a specimen taken from a necrotic focus were found to be negative for tubercle bacilli.

Case 3: The patient was a white male who had been employed in the hard-coal mines for approximately thirty years. He had had preoperative chemotherapy for nine months. Pulmonary function studies of a ventilatory nature were normal. On November 29, 1956, when the patient was sixty-six years of age, an extraperiosteal plombage with Lucite balls was performed on the right to close a cavity in the right upper lobe. The plombage was done instead of a resection of the upper lobe because of his rather advanced age. The postoperative course was uneventful.

The patient was last seen on May 31, 1957, about six months postoperatively; he has been noninfectious since the operation. The roentgenograms since the plombage have shown no evidence of cavity. The patient is still receiving chemotherapy which probably will be continued for eighteen months after the surgery.

Case 4: The patient was a white male who had been a hard-coal miner for approximately twenty years. He had had preoperative chemotherapy for about thirteen months. Preoperative ventilatory studies showed some impairment of ventilation, obstructive in type; bronchospirometry showed the right lung to be performing approximately 55 per cent of the ventilation. On March 10, 1955, when the patient was sixty years of age, the apical segment of the right upper lobe containing a cavity was removed. The postoperative course was uneventful. He received chemotherapy for one year postoperatively.

The patient was last seen on March 12, 1957, one year after completion of drug therapy and about two years after surgery; his bacteriologic examinations have all been negative. Material taken from the cavity in the resected specimen was negative for tubercle bacilli on microscopy and culture.

Case 5: The patient was a white male who had been employed in the hard-coal mines for about fifteen years. Presurgical ventilatory studies showed some impairment of ventilation, restrictive in character. After the patient received chemotherapy for twelve months, a two-stage right upper lobe thoracoplasty was done in May, 1956, to close a cavity in the right upper lobe. The collapse procedure was done instead of a resection of the upper lobe as it was thought at this time that he possibly had contralateral cavitary disease. Because the sputum continued to be infectious, on October 18, 1956, when the patient was forty-six years of age, he had a right upper lobectomy; the resected specimen showed a cavity. Chemotherapy is still being continued.

The patient was last seen on May 22, 1957, about seven months after the resectional surgery; he showed intermittently infectious sputum until March,

TABLE 4

COMBINED THERAPY IN 6 PATIENTS WITH SILICOTUBERCULOSIS

Case Number	Age	Chemotherapy Before Surgery	Surgery	Chemotherapy After Surgery	Reversal of Infectiousness
	years	*months*		*months*	
1	56	12	Lobectomy	12	Yes
2	44	48	Pneumonectomy	18	Yes
3	66	9	Plombage	6*	Yes
4	60	13	Removal of segment	12	Yes
5	46	12	Thoracoplasty followed by lobectomy	7*	No
6	67	17	Plombage	8*	No

* Chemotherapy has not been completed.

1957. In April and May, 1957, the bacteriologic examinations were negative for tubercle bacilli. No cause for the infectious sputum was found, bronchoscopy revealing a normal tracheobronchial tree, and planigrams of both lungs showing no evidence of cavitary disease.

Case 6: The patient was a white male who had been a hard-coal miner for thirty-five years. Because he initially refused thoracic surgery, he had had preoperative chemotherapy for seventeen months. Presurgical ventilatory studies were satisfactory. On September 13, 1956, when he was sixty-seven years of age, a left plombage thoracoplasty with Lucite balls was performed to collapse a rather large cavity in the left upper lobe which had apparently arisen from a conglomerate mass. Because of his rather advanced age, the collapse procedure was done instead of resection. The postoperative course was uneventful; he is still being continued on chemotherapy.

The patient was last seen in May, 1957, about eight months after surgery; his sputum has been intermittently infectious. However, serial roentgenograms of the chest have shown that the cavity, although still present, is much smaller.

Most of the data given in the case reports are summarized in table 4. The results of combined therapy were superior to those of chemotherapy alone. All of the patients have had fair pulmonary reserve postoperatively and none could be regarded as a pulmonary cripple. The postoperative bacteriologic results can be summarized in the following manner: reversal of infectiousness without relapse occurred in 4 patients, in 3 who had resections and one a plombage; these 4 patients had been followed postoperatively from six to twenty-nine months. In the other 2 patients (one who had a lobectomy preceded by a thoracoplasty, and the other a plombage), who were followed from seven to eight months postoperatively, reversal of infectiousness did not occur. In the lobectomy case, no cause was found for the infectious sputum for the first five months of the postoperative period. In the plombage case, the infectious sputum was accounted for by the uncollapsed cavity. It may be seen that the results of the resectional procedures were better than those of the collapse variety.

After examination of the resected specimens of the lungs in *Cases 1*, *2*, and *4*, Dr. O. Auerbach, Chief of the Laboratory Service of the Veterans Administration Hospital, East Orange, New Jersey, where the resections were done, made similar

comments with regard to each specimen. According to him, the anatomic findings showed favorable effects of chemotherapy similar to those seen in nonsilicotic phthisis. There was a greatly decreased perifocal reaction around the tuberculous cavity and the tuberculous foci, a decrease in fibrous tissue formation about the tuberculous disease, and evidence of healing of the cavity. In addition, in each case, evidence of silicosis was found. It should be noted that in 2 of the 3 cases, although the bacteriologic examination of the sputum was positive for tubercle bacilli before surgery, the smears and cultures from two of the resected specimens were negative. It should be realized that these negative results were obtained on material taken from a small area of each specimen.

Discussion

Briefly stated, this was a study of the roentgenographic and bacteriologic effects of therapy in a group of 25 patients with extensive silicotuberculosis. Previously untreated, this group consisted of 19 patients who received chemotherapy alone, chiefly with streptomycin and isoniazid, and of 6 patients with unilateral cavitary disease who, in addition, had various surgical chest procedures.

A comparison of the results of chemotherapy in patients with silicotuberculosis (apparently the first group of the patients in the present study who were treated with isoniazid as one of the chemotherapeutic agents) with those of others would be valuable. In a study devoted particularly to the clinical features of approximately 100 patients with silicotuberculosis, Theodos and Gordon (4) found that streptomycin and PAS were roentgenographically and bacteriologically ineffective in the therapy of this disease. Cohen and Glinsky (5), administering only streptomycin to 18 patients for a period of one year, also observed extremely unfavorable results: only one of their patients showed roentgenographic improvement and not one patient displayed reversal of infectiousness. In contrast to the results of the previous two studies, Moyer (6), who treated 13 patients with streptomycin and PAS for periods up to one year, found roentgenographic regression in 10 and reversal of infectiousness in 5 patients. The results of the present writers with regard to roentgenographic improvement and reversal of infectiousness were better than those of the first two reports, but not as good as Moyer's despite the fact that isoniazid was one of the chemotherapeutic agents in the present regimens.

A comparison of the results of chemotherapy in nonsilicotic phthisis with those of chemotherapy of the patients in the present report is inevitable. That the former results are far superior from the standpoint of cavity closure and reversal of infectiousness is exemplified by the studies of Pitts and his co-workers (7) with streptomycin and isoniazid, and of Jimenez (8) with isoniazid alone, to mention just a few. The relatively poor results in the cases of the present report may be explained by the fact that therapy was directed at extensive chronic silicotuberculosis in which closure of cavity is impeded by fibrosis and loss of pulmonary elasticity as a result of emphysema.

As in nonsilicotic tuberculosis, chemotherapy in these patients has resulted in

instances of the "open-negative" cavity and the "filled-negative" cavity. These effects of chemotherapy on the cavity are much less desirable than cavity closure since relapse of the tuberculous disease, particularly after discontinuation of the chemotherapy, is more apt to occur in instances of open- or filled-negative cavity.

That patients with silicotuberculosis can be operated on successfully should not elicit surprise. Other writers have reported successful resectional procedures in such patients. Of the group of patients reported by Moyer (6), one had a segment of lung removed. In addition, in 1947, Woodruff and Kelly (9) reported a case in which a right pneumonectomy was performed for a large mass considered to be a neoplasm; however, examination of the specimen revealed a tuberculous conglomerate mass in the right lower lobe and evidence of second-stage silicosis in the rest of the lung. Furthermore, in 1955, Chapman and Bumgarner (10) reported a case of silicotuberculosis in which two segments of the right upper lobe were removed. Although limited, the experience of others just recounted and that of the present writers should serve to make clear that the patient with silicotuberculosis is not always a pulmonary cripple to be relegated to the medical sidelines; that with chemotherapy he can survive a surgical procedure on the chest; that he can recover from tuberculosis; and that he can be left with fair pulmonary reserve. In addition, the experience of the present writers would indicate that without further cavity closure after chemotherapy for six months, and with roentgenographic deterioration becoming quite manifest with more prolonged therapy, thoracic surgery, if feasible, should be carried out soon after the six-month period.

The present results with the medical-surgical approach to rather extensive tuberculosis in silicosis, from the standpoint of cavity eradication along with reversal of infectiousness, were good. Results with chemotherapy alone from this standpoint left much to be desired. Unfortunately, many of the patients, chiefly because of their pulmonary disability, could not enjoy the benefits of surgery. What can be done to prevent the misfortune which befell a large segment of this group of patients? Aside from the institution of dust-control measures to prevent silicosis, every effort should be exerted to recognize the tuberculous infection in an early phase and to treat it. Such recognition will depend upon familiarity with the three roentgenographic patterns of silicosis. It is generally accepted that the lesions of first- and second-stage silicosis, namely, increased striations and nodulation, are probably not tuberculous. A high percentage of conglomerate disease of third-stage silicosis, however, is thought to be of this nature (11, 12), but the experience of the present writers has shown that in such disease tubercle bacilli are infrequently recovered from the sputum. Through periodic roentgenograms of workers exposed to a silica hazard, conglomeration in its initial stages can be recognized. If it is progressive, if other disease is excluded, and if the tuberculin test is positive, the lesion should be regarded as tuberculous and chemotherapy, possibly with isoniazid, should be instituted if only to prevent further conglomeration.

Summary

A study is presented of the roentgenographic and bacteriologic effects of therapy in a group of 25 patients with extensive silicotuberculosis. Previously untreated, this group consisted of 19 patients who received chemotherapy alone, chiefly streptomycin and isoniazid; and of 6 with unilateral cavitary disease who, in addition, had various thoracic surgical procedures.

The results of chemotherapy alone from the standpoint of cavity closure along with reversal of infectiousness were poor as compared with those for patients with nonsilicotic phthisis. The results of chemotherapy and surgery in the 6 patients were good, particularly with the resectional procedures.

If chemotherapy alone is to play a significant role in silicotuberculosis, it would appear advisable to regard conglomerate disease in its initial stages as tuberculous, in the presence of a positive tuberculin test, and to treat it as such if only to prevent further conglomeration.

Sumario

Silicotuberculosis: Resultados de la Terapéutica Médica y de la Médicoquirurgica Combinada

Preséntase un estudio de los efectos radiográficos y bacteriológicos de la terapéutica en un grupo de 25 enfermos que padecían de silicotuberculosis difusa. Sin tratamiento anterior, este grupo constaba de 19 enfermos que recibían solamente quimioterapia, principalmente estreptomicina e isoniacida, y de 6 que tenían afección cavitaria unilateral y habían sido además objeto de varios procedimientos quirúrgicos.

Los resultados de la quimioterapia sola, desde el punto de vista de clausura de las cavernas y del viraje bacteriológico, fueron malos, comparados con los obtenido en los enfermos que tenían tisis no silicótica. Los resultados de la quimioterapia y la cirugía en los 6 enfermos fueron buenos, en particular con los procedimientos de resección.

Si la quimioterapia sola va a desempeñar un papel importante en la silicotuberculosis, parecería conveniente considerar a la enfermedad conglomerada en sus etapas iniciales como tuberculosa se existe una reacción positiva a la tuberculina, y tratarla como tal aunque no fuera más que para impedir mayor conglomeración.

Resume

Silico-tuberculose: Résultats du traitement médical et médico-chirurgical combinés

Présentation d'une étude sur les effets radiologiques et bactériologiques du traitement dans un groupe de 25 malades atteints de silico-tuberculose extensive. Ce groupe, non traité antérieurement, comprenait 19 patients, qui ont été soumis à la chimiothérapie seule, principalement avec la streptomycine et l'isoniazide, et 6 malades avec lésions cavitaires unilatérales, qui ont en plus subi diverses interventions chirurgicales.

Les résultats de la chimiothérapie seule du point de vue de l'oblitération cavitaire en même temps de celui de la "négativité" bactériologique n'étaient pas bons par comparaison avec ceux obtenus dans les cas de tuberculose sans silicose. Les résultats de la chimiothérapie avec intervention chirurgicale chez les six malades étaient bons, en particulier dans les cas avec résection.

Si la chimiothérapie seule doit jouer un rôle significatif en silico-tuberculose, il paraît préférable de considérer la double maladie lors de son premier stade comme une tuberculose, lorsque le test à la tuberculine est positif, et la traiter comme telle, ne serait-ce que pour prévenir les progrès de cette combinaison pathologique.

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Addendum

Unfortunately not mentioned was the article by Andrews and associates (13), reporting 14 patients with silicotuberculosis who were treated both medically and surgically. Thirteen patients had resectional procedures and one, an extraperiosteal plombage. The course of the 14 was followed for one to five years; 8 of these patients were considered to have arrested disease.

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THE FREQUENCY OF POSTPRIMARY PULMONARY TUBERCULOSIS ACCORDING TO PULMONARY ARTERIAL PRESSURE[1]

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Introduction

Whether or not certain cardiac valvular defects confer increased resistance to pulmonary tuberculosis, while others predispose to this disease, is a question which has been discussed for more than a century. No uniform opinion has been reached, however. The literature which has accumulated seems to be less elucidative than might be assumed from its extensiveness.

Review of the Literature

Although some writers had already drawn attention to the coexistence of pulmonary tuberculosis and stenosis of the pulmonary valve, Rokitansky (1) opened the debate in earnest in 1846 by presenting his theory that cardiac disease with pulmonary congestion precludes pulmonary tuberculosis.

Some clinical series of valvular heart disease and pulmonary tuberculosis are frequently cited. Most of these series are of fairly early date and a number are very large. They are based solely on physical examination, however, and therefore lack major evidential force (2–9). Reports which failed to differentiate between types of cardiac disorder may likewise be disregarded (10, 11).

Some autopsy investigations are weakened by failure to describe the type and severity of the anatomic changes in the cardiac and tuberculous conditions. A number of writers themselves express doubt that the anatomic exploration was made with adequate thoroughness. Others have attempted to show, with the aid of the records in autopsy cases, whether mitral disease or pulmonary tuberculosis was first present (2, 15). This, for the modern reader, seems foredoomed to failure.

What chiefly diminishes the value of many reports of clinical or autopsy series, however, is the absence of statistical confirmation or of acceptable control material (12–22).

In recent decades the question has been more precisely formulated, and interest has become centered on mitral and pulmonary stenosis. The hypothesis that mitral disease precludes pulmonary tuberculosis has gradually been abandoned, and case reports of their coexistence have become less frequent.

After surveying the available literature on the relationship between cardiac defects and pulmonary tuberculosis, the writer concentrated, for the reasons stated above, on a few reports. He then found that these yielded some support for the old concept that the frequency of pulmonary tuberculosis is lower in persons with mitral stenosis and higher in those with pulmonary stenosis than in the general population.

Tileston (23) thus stated that active pulmonary tuberculosis was present in 10 per cent of 1,900 consecutive autopsies from a Boston hospital, but was not found in any of the 66 cases of mitral stenosis included in the series. In 1,811 autopsies from another

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Boston hospital during the same period, the frequency of active pulmonary tuberculosis was 8.3 per cent; the 54 persons with mitral stenosis included 2 with active pulmonary tuberculosis. The two series together contained 67 cases of severe mitral stenosis. None of these patients had active pulmonary tuberculosis, although the frequency of that disease in the combined total series was 9 per cent.

Neuman (24) reviewed all of the autopsy reports from the Institute of Pathologic Anatomy in Vienna for the year 1908. Of the 1,767 cases, 22.2 per cent had "open"[2] pulmonary tuberculosis. The corresponding figure for the 120 cases of mitral disease included in the series was 5.8 per cent. Extrapulmonary tuberculosis was found in 3.7 per cent of the series as a whole and in 3.3 per cent of the patients with mitral defects.

Soulié, Bouvrain, di Mattéo, and Rey (25) investigated the incidence of tuberculosis in all patients with cardiac malformations at two clinics in Paris. Of these 694 patients, 19 had active pulmonary tuberculosis confirmed by bacteriologic examination. The type of cardiac defect was ascertained by contrast roentgenography and heart catheterization. In the various forms of pulmonary stenosis, tuberculosis was three times as common as in the other patients.

It is not entirely clear how the clinical material was obtained in some reports on pulmonary stenosis and tuberculosis. Nevertheless, it seems improbable that such high figures for coexistence as 80, 30, and 22 per cent could be reached unless there was, in fact, a higher incidence of pulmonary tuberculosis than in the general population (2, 5, 26).

It is not primarily the practical clinical importance of concomitant cardiac disorder and pulmonary tuberculosis that has maintained the interest in this combined disease. Rather, it is the concept that elucidation of the coexistence frequency might reveal the pulmonary circulation as a central factor in the pathogenesis of postprimary pulmonary tuberculosis. Narrowing of the mitral or the pulmonary valve may entail severe and constant changes in the pulmonary circulation, with elevated pressure in the former case and low pressure in the latter. In other words, the development of postprimary pulmonary tuberculosis may be favored in some way by low pulmonary arterial pressure and counteracted by high pressure.

That the pulmonary circulation indirectly is an important factor in the development of postprimary pulmonary tuberculosis is also the idea underlying the theory which was most fully elaborated by Dock (27) to explain the initially apical location of the lesions. The relatively low pulmonary arterial pressure in erect man, according to this theory, involves heightened oxygen tension in the upper regions of the lungs. In this environment, the growth of tubercle bacilli may be favored, thus assisting them to overcome the body's defenses and establish disease in the lung. The basis of the hypothesis comprises theoretic calculations of the influence of orthostatic pressure on the peripheral pulmonary circulation (27), *in vitro* experiments with tubercle bacilli (28–30), and *in vivo* tests (31–33). It has gained further probability from recent research in pulmonary physiology (34–36). This modern theory would seem to be easily compatible with the old assumption that the difference in pulmonary arterial pressure in stenosis of the mitral valve and in pulmonary stenosis is the cause of the postulated variation in the frequency of pulmonary tuberculosis.

The present report describes yet another attempt to elucidate the question of pulmonary tuberculosis in organic heart disease. In view of the above reasoning, it seemed appropriate to proceed from a series of persons with cardiac disease and to correlate the frequency of tuberculosis with the pressure in the pulmonary

[2] By "open" Neuman seems to imply "active" tuberculosis.

artery, as measured at heart catheterization, instead of with the type of cardiac defect. Significant alteration of pressure is not necessarily present in cardiac disease, and only catheterization yields accurate information of the pressure conditions.

Material

The material of the study was obtained from two cardiac clinics in Stockholm which accept patients from all of Sweden. All cases of congenital cardiac anomaly or of mitral disease in which heart catheterization was performed during the years 1948 to 1956 were reviewed. The series was confined to persons more than fifteen years old who were born and brought up in Sweden. Most of these *413* persons had been referred to the clinics with a view to surgical relief of the cardiac defect.

A search was made for pulmonary lesions compatible with present or past postprimary tuberculosis. For this purpose, the reports from the roentgenographic examination to which all patients were submitted at the time of catheterization were reviewed. When the reports suggested or described pulmonary lesions, the roentgenograms were studied. The case notes of all patients were also searched for a history of pulmonary tuberculosis. *Fourteen* patients showed or had shown roentgenographic signs of postprimary pulmonary tuberculosis.

According to the *mean pressure* in the pulmonary artery, the series was thereafter divided into three groups: patients with high, normal, or low pressure. Normal readings were considered to lie between 14 and 20 mm. of mercury during rest. Mean pressure in excess of 20 mm. was thus regarded as high, and persons with readings of less than 14 mm. were included in the hypotensive group. In the cases in which a water manometer was used, the pressure was recalculated to millimeters of mercury. In 14 cases in which the mean pressure had not been calculated or was not recorded, the arithmetic mean was used instead. No figures were available for 18 cases; instead a brief report, such as "normal pressure in the pulmonary circulation" or "pathologically elevated pressure," decided the group in which the patient was placed.

When a light or moderate work load involved a rise of mean pressure to at least 30 mm. of mercury, the patient was included in the hypertensive group, even if the mean resting pressure had been within the limits classed as normal. In 2 patients the catheter could not enter the pulmonary artery. These patients had congenital cardiac anomalies and pulmonary tuberculosis; infundibular pulmonary stenosis of extreme severity was demonstrated by angiocardiography. Since all experience indicates that in such cases the pulmonary arterial pressure is very low, it was considered warrantable to class the patients as hypotensive, despite the absence of figures.

The pulmonary arterial pressures registered in the hypertensive patients ranged from 21 to 139 mm. of mercury. A rough classification of the pressure levels within this group is shown in table 1.

The distribution of the most common congenital cardiac anomalies according to pulmonary arterial pressure may be seen in table 2.

TABLE 1

Mean Pressure in the Pulmonary Artery in Hypertensive Patients

	Pulmonary Arterial Pressure (mm. Hg.)			Total
	21–30	31–50	51–139	
Number of Patients.....	120*	88	53	261

* Includes patients with normal pressure at rest, but with at least 30 mm. of mercury during light or moderate work.

TABLE 2

MOST COMMON CONGENITAL CARDIAC DEFECTS IN THE CLINICAL MATERIAL DISTRIBUTION ACCORDING TO PULMONARY ARTERIAL PRESSURE

Cardiac Defects	Hypertensive Patients		Normotensive Patients		Hypotensive Patients	
	All Patients	With Tuberculosis	All Patients	With Tuberculosis	All Patients	With Tuberculosis
Patent ductus arteriosus	30		28		4	
Atrial septal defect	20		24	1	8	
Pulmonic stenosis			5		20	3
Fallot's tetralogy			6	1	18	4
Ventricular septal defect	12		8			
Eisenmenger's complex	14					

TABLE 3

OCCURRENCE OF POSTPRIMARY PULMONARY TUBERCULOSIS IN CARDIAC PATIENTS DISTRIBUTION ACCORDING TO PULMONARY ARTERIAL PRESSURE

Age Group	Hypertensive Patients						Normotensive Patients						Hypotensive Patients					
	All Patients			With Tuberculosis			All Patients			With Tuberculosis			All Patients			With Tuberculosis		
	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total
15–19	4	17	21				12	13	25				8	12	20			
20–24	7	18	25				6	13	19				7	10	17		1	1
25–29	13	15	28				5	12	17				4	6	10	1	1	2
30–34	8	27	35				4	6	10	1	1	2	2	3	5	2		2
35–39	16	35	51		2	2	3	4	7				1	1	2		1	1
40–44	9	35	44				1	3	4		1	1	2	4	6		1	1
45–49	8	22	30				2	1	3									
50–54	8	15	23	1		1	3	3	6					1	1		1	1
55–59	2	1	3															
60–64	1		1															
Total	76	185	*261*	1	2	*3 (1%)*	36	55	*91*	1	2	*3 (3%)*	24	37	*61*	3	5	*8 (13%)*

RESULTS

The distribution according to pulmonary arterial pressure of the series as a whole and of the tuberculosis cases is presented in table 3.

The 261 hypertensive patients thus included 3 (1 per cent) with postprimary pulmonary tuberculosis. All 3 had been hospitalized for active disease. In one the lesions were moderately advanced, and in 2 they were minimal.

Case 1. H. A., a 37-year-old female, was examined at the cardiac clinic in January, 1955. The diagnosis was mitral stenosis and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 35 mm. of mercury.* The cardiac defect had been recognized since early school age. Pulmonary lesions were detected in 1941, when the roentgenogram showed scattered,

mottled, and streaky opacities in the upper field of the left lung and behind the first right rib. The patient received sanatorium treatment. In May, 1955, a guinea pig test of gastric washings was positive for tubercle bacilli. Sanatorium treatment was repeated.

Case 2. W. L., a 35-year-old female, was examined at the cardiac clinic in February, 1955. The diagnosis was mitral stenosis, pulmonary tuberculosis, and diabetes mellitus. *The mean pulmonary arterial pressure was 31 mm. of mercury.* The cardiac disorder was found when the patient was twelve years old. In 1926, she had had right exudative pleurisy. In 1941, pulmonary roentgenograms showed a hazelnut-sized, excavated, round lesion in the second left intercostal space. This was treated with artificial pneumothorax. In 1954, left apical spread occurred, and the sputum contained acid-fast bacilli. The patient was readmitted to the sanatorium.

Case 3. B. K., a 50-year-old male, was examined at the cardiac clinic in May, 1956. The diagnosis was mitral stenosis and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 26 mm. of mercury.* In 1924, the patient had had rheumatic fever, and in 1942 *gastric resection* was performed. Roentgenographic examination of the lungs in 1951 revealed small groups of mottled opacities in the first and second right intercostal spaces. The sputum contained acid-fast bacilli, and the Mantoux test was positive. Artificial pneumothorax was given.

Of the 91 normotensive patients, 3 (3 per cent) showed roentgenographic evidence of postprimary pulmonary tuberculosis. One had been hospitalized for active, moderately advanced tuberculosis and the others had minimal, probably inactive lesions.

Case 4. L. E., a 41-year-old female, was examined at the cardiac clinic in December, 1949. The diagnosis was atrial septum defect and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 19 mm. of mercury.* The pulmonary lesions were discovered in 1931. Both apices then showed well-defined streaky and mottled opacities. The Mantoux test was positive. Bacteriologic tests were not performed. The roentgenographic appearance was unchanged in 1949.

Case 5. J. H., a 34-year-old female, was examined at the cardiac clinic in January, 1954. The diagnosis was Fallot's tetralogy and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 15 mm. of mercury.* Pulmonary roentgenograms in 1954 showed scattered, slight, and well-defined opacities in both apices. The Mantoux test was positive. The bacterial findings are not known. The patient was placed under observation for tuberculosis.

Case 6. M. H., a 34-year-old male, was examined at the cardiac clinic in May, 1955. The diagnosis was mitral stenosis and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 15 mm. of mercury.* At the age of eighteen the patient had had rheumatic fever. Hemoptysis occurred in 1955. Roentgenographic examination then revealed diffuse excavating lesions in the apex of the left lung. The Mantoux test was positive and the sputum contained acid-fast bacilli. He was admitted to the sanatorium.

The 61 hypotensive patients comprised 8 (13 per cent) with lesions of postprimary pulmonary tuberculosis. Seven had received sanatorium treatment for active tuberculosis; in one, the disease was far advanced; in 6, it was moderately advanced. The eighth patient had moderately advanced, probably inactive lesions.

Case 7. S. E., a 26-year-old female, was examined at the cardiac clinic in February, 1953. The diagnosis was Fallot's tetralogy and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 6 mm. of mercury.* In 1952, the patient became acutely ill, and pulmonary roentgenograms showed diffuse parenchymal opacity and cavitation in the upper lobe of the right lung. A guinea pig test of gastric washings was positive for tubercle bacilli. The patient was admitted to the sanatorium.

Case 8. H. O., a 35-year-old female, was examined at the cardiac clinic in February, 1953. The diagnosis was valvular pulmonary stenosis, atrial septum defect, and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 7 mm. of mercury.* Roentgenographic examination following hemoptysis in 1944 revealed confluent, diffuse opacities in the upper field of the left lung and a large apical cavity. A guinea pig test of gastric washings was positive for tubercle bacilli. The patient received sanatorium treatment.

Case 9. L. A., a 31-year-old male, was examined at the cardiac clinic in April, 1953. The diagnosis was valvular pulmonary stenosis and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 8 mm. of mercury.* Hemoptysis occurred in 1953, and roentgenograms showed streaky, mottled, and confluent lesions within the entire upper field of the left lung, with an apical cavity. Acid-fast bacilli were found in many sputum samples. Pulmonary resection was performed. Histologic examination of the resected tissue confirmed the diagnosis.

Case 10. W. I., a 24-year-old female, was examined at the cardiac clinic in November, 1954. The diagnosis was valvular pulmonary stenosis and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 6 mm. of mercury.* During an acute illness in 1948, the patient was found to have coarsely mottled, diffuse opacities throughout the left lung, with apical cavitation. The right upper lobe contained mottled and atelectatic lesions and a cavity. Acid-fast bacilli were repeatedly recovered from the sputum. The treatment consisted of artificial pneumothorax.

Case 11. E. G., a 28-year-old male, was examined at the cardiac clinic in November, 1954. The diagnosis was Fallot's tetralogy with dextrocardia and pulmonary tuberculosis. *Angiocardiography revealed stenosis of the conus arteriosus* with a septum 1 cm. thick. The width of the pulmonary artery lumen was scarcely half of normal. The heart catheter could not be guided into the pulmonary artery. Intraventricular pressure was high. When the patient became acutely ill in 1951, roentgenographic examination showed cloudy, confluent, and excavating lesions within the upper region of the left lung. A guinea pig test with sputum was positive for tubercle bacilli. Artificial pneumothorax was given.

Case 12. B. R., a 42-year-old female, was examined at the cardiac clinic in January, 1955. The diagnosis was Fallot's tetralogy and pulmonary tuberculosis. *Angiocardiography showed severe infundibular stenosis of the pulmonary artery.* The catheter could not be passed into the pulmonary artery. Intraventricular pressure was high. At roentgenographic examination in December, 1954, small, mottled, and streaky lesions with parenchymal retraction were seen in both upper lung fields. The Mantoux test was positive. Bacterial tests were not made. The roentgenogram was unchanged in 1955.

Case 13. A. J., a 32-year-old male, was examined at the cardiac clinic in February, 1955. The diagnosis was Fallot's tetralogy and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 12 mm. of mercury.* When the patient became acutely ill in 1947, roentgenographic examination disclosed small, slight lesions in the apices of both lungs. In the left midfield there was a larger opacity surrounded by mottling. A guinea pig test of gastric washings was positive for tubercle bacilli. The patient received sanatorium treatment.

Case 14. L. M., a 52-year-old female, was examined at the cardiac clinic in May, 1955. The diagnosis was cardiac defect, possibly mitral, and pulmonary tuberculosis. *The mean pulmonary arterial pressure was 12 mm. of mercury.* In 1930 acute symptoms led to the discovery of small, mottled lesions in both pulmonary apices and a confluent, diffuse infiltration extending from the fourth to the sixth left intercostal space. Löwenstein culture of the sputum showed tubercle bacilli. The treatment was artificial pneumothorax.

The frequency of postprimary pulmonary tuberculosis in the patients with normal pulmonary arterial pressure was 10 per cent lower than that in the hypotensive group. The difference was statistically significant ($\chi^2 = 5.24$.)[2] The tuberculosis frequency in the hypotensives was likewise significantly higher than in the hypertensives ($\chi^2_c = 17.98$.)[2]

The 1 per cent incidence of postprimary pulmonary tuberculosis in the hypertensive patients, on the other hand, was not significantly different from the 3 per cent in the normotensive patients.

Discussion

The number of tuberculous persons in the series as a whole could have been influenced by whether the physicians who referred patients to the cardiac clinics were inclined to do so irrespective of concomitant tuberculosis. It is difficult, however, to find reasons why this potential variation should not have been similar in all types of cardiac disease. One may therefore assume that it did not distort the tuberculosis frequency within the three "pressure groups."

Pulmonary lesions of the type which in clinical tuberculosis practice are described as "calcified primary complex" were found in 7 per cent of the patients with high pulmonary arterial pressure, in 3 per cent of the normotensive, and in 2 per cent of the hypotensive patients. The higher figure for the hypertensives may be regarded as suggestive of greater incidence of tuberculous infection in that group. At any rate, these figures give no reason to deduce more frequent primary infection in the hypotensive and normotensive patients than in the hypertensive group.

The tuberculosis morbidity in the provinces from which the patients were referred to the cardiac clinics varied during the period covered by the study, as shown by the official figures for mortality and first hospitalizations for tuberculosis. On the basis of these figures, the Swedish provinces were divided into three groups according to tuberculosis incidence. The percentage distribution of the patients with regard to pulmonary arterial pressure and home province is shown in table 4. The normotensive and hypotensive patients were similarly distributed, while the hypertensive patients derived to a somewhat greater extent from regions with the highest tuberculosis frequency. If anything, this should have implied greater likelihood of tuberculosis in the hypertensive patients.

The circulatory "shunts" which complicate some congenital cardiac defects may be thought to contribute in some way to the development of postprimary pulmonary tuberculosis. It was therefore considered of interest to observe how

[2] The chi-square test was used for comparing observed tuberculosis frequencies. As a rule, Yates' correction was necessary (χ^2_c).

TABLE 4

DISTRIBUTION OF CARDIAC PATIENTS ACCORDING TO TUBERCULOSIS FREQUENCY IN HOME PROVINCE

Pulmonary Arterial Pressure (Patient Group)	Tuberculosis Frequency in Home Province			Total
	High	Moderate	Low	
	per cent	*per cent*	*per cent*	*per cent*
High	62	20	18	100
Normal	56	18	26	100
Low	56	17	27	100

the various types of congenital cardiac anomaly were distributed according to pulmonary arterial pressure. This may be seen in table 2. Defects which entail shunt were most common in the patients with high pulmonary arterial pressure. No patient with such a defect and high pressure had pulmonary tuberculosis. Of the 7 patients with tuberculosis and low pulmonary arterial pressure, 3 had isolated pulmonary stenosis. The hypotensive group included 18 patients with Fallot's tetralogy, 4 of whom also had pulmonary tuberculosis. The 14 hypertensive patients with the type of ventricular septal defect in which the "shunt" mechanism is of essentially the same type as in Fallot's tetralogy (Eisenmenger complex) were all without signs of postprimary pulmonary tuberculosis. There was thus no evidence that cardiac defects with pathologic communication between the systemic and pulmonary circulations were responsible for the differences in tuberculosis frequency between the "pressure group."

The age and sex of all of the patients are seen in table 3. In contrast to the patients with normal or low pulmonary arterial pressure, most of the hypertensive patients were in the older age groups. Since, in the lifetime of all of the patients, the general frequency of tuberculosis has steadily declined, the higher median age of the hypertensive patients should, in fact, have entailed greater risk of tuberculosis than in the other patients. If the frequency of tuberculosis is studied in the age groups of hypertensive and normotensive patients in which this disease was found, i.e., thirty years and older, a significantly lower frequency is seen in the hypertensive group ($\chi^2_c = 4.02$.)[3] As tuberculosis was not observed in the younger hypertensive patients, it is also unlikely that its incidence in the older patients was appreciably reduced by deaths from tuberculosis. The fact that no hypertensive patient younger than thirty-five had tuberculosis, while the disease was present in 5 patients from the smaller corresponding age group of hypotensive patients, shows also that the age factor did not contribute to the difference in tuberculosis frequency with regard to these groups. Comparison of the age groups with ten-year intervals in the normotensive and hypotensive patients shows that the tuberculosis frequency was considerably higher, both absolutely and relatively, in the latter. When the age factor is taken into account, therefore, the difference in tuberculosis frequency between normotensive and hypertensive patients and between normotensive and hypotensive patients becomes still more clear.

At all levels of pulmonary arterial pressure, there were more women than men. The difference was greatest in the patients with high pressure. Within the groups of pressure, however, the sex ratio in the various ages was fairly constant. The tuberculosis frequency in each of the three groups showed a similar sex ratio for the group as a whole and within the various age classes. The circumstance that the hypertensive group, both relatively and absolutely, comprised more older women than the other groups cannot have contributed to the lower tuberculosis frequency in the hypertensive patients as, according to the official annual morbidity figures, the collective risk of developing tuberculosis in such ages was similar for both sexes. Thus, the sex factor also fails to explain the observed differences in tuberculosis frequency.

Summary

The frequency of postprimary pulmonary tuberculosis was investigated in 413 patients with congenital cardiac anomalies or with mitral disease.

The patients were classified according to the pressure in the pulmonary artery. This pressure was high in 261 patients, normal in 91, and low in 61.

Postprimary pulmonary tuberculosis was present in 1 per cent of the hypertensive patients, in 3 per cent of the normotensive group, and in 13 per cent of the hypotensive group.

The difference in tuberculosis frequency (10 per cent) between the normotensive and the hypotensive patients was statistically significant. The corresponding difference (12 per cent) between the hypertensive group and the hypotensive group was likewise significant.

Between the normotensive and the hypertensive groups the difference in tuberculosis frequency (2 per cent) was not statistically significant.

Sumario

La Frecuencia de la Tuberculosis Pulmonar Postprimaria de Acuerdo con la Presión Arterial Pulmonal

En 413 enfermos que tenían anomalías cardíacas congénitas o padecían de afección mitral, se investigó la frcuencia de la tuberculosis pulmonar postprimaria.

Se clasificó a los enf rmos de acuerdo con la tensión observada en la arteria pulmonar. Esta tensión fué alta en 261 enfermos, normal en 91 y baja en 61.

Había tuberculosis pulmonar postprimaria en 1 por ciento de los hipertensos, 3 por ciento del grupo normotenso y 13 por ciento del grupo hipotenso.

La diferencia (10 por ciento) en la frecuencia de la tuberculosis entre los enfermos normotensos y los hipotensos revistió importancia estadística. La diferencia correspondiente (12 por ciento) entre el grupo hipertenso y el hipotenso fué también importante.

La diferencia (2 por ciento) en la frecuencia de la tuberculosis entre el grupo normotenso y el hipertenso no fué importante estadísticamente.

Resume

Fréquence de la tuberculose pulmonaire post-primaire par rapport à la pression dans l'artère pulmonaire

La fréquence de la tuberculose pulmonaire post-primaire a été l'objet d'une investigation chez 413 malades présentant des anomalies cardiaques congénitales ou une maladie mitrale.

Les malades ont été classifiés sur la base de la pression artérielle dans l'artère pulmonaire. Cette pression était élevée chez 261 malades, normale chez 91 et basse chez 61.

La tuberculose pulmonaire post-primaire était présente dans 1 pour cent des cas avec hypertension, dans 3 pour cent des cas à tension normale et dans 13 pour cent des cas avec hypotension.

L'écart dans la fréquence de la tuberculose (10 pour cent) entre les cas à tension normale et ceux à tension basse est significatif du point de vue statistique. L'écart correspondant (12 pour cent) entre le groupe avec hypertension et le groupe avec hypotension était également significatif. L'écart dans la fréquence de la tuberculose (2 pour cent) entre les groupes à tension normale et les groupes avec hypertension était dépourvu de signification statistique.

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LOCAL REACTIVATION OF THE PRIMARY TUBERCULOUS FOCUS IN THE LUNG[1]

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INTRODUCTION

In the vast majority of cases, the primary infection in man with *M. tuberculosis* takes place in the lung. The primary complex thus caused always shows a certain monotony, both clinically and anatomically. In particular, the primary pulmonary focus exhibits a marked tendency to a stereotyped course. Complications due to the progressive nature of the tuberculous inflammation in the regional lymph nodes being fairly frequent, the pulmonary focus usually subsides without incident and very often ends as quite a respectable calcified focus. However, occasionally cases are seen in which the primary focus is progressive. Such local extensions occur in two categories. First, extensions of the primary focus are seen when it has not yet subsided (*type I*). More interesting, but also rarer, are those cases in which the pulmonary focus has reactivated when the primary complex has been quiet and unchanged for years (often containing calcium), and the patient meanwhile has been considered to be healthy (*type II*).

In the more recent literature this type of reactivation is hardly touched upon. Apart from a few English and French case reports, which cannot always bear criticism, only Neuenschwander's article (1) is worth mentioning. In that paper, seven cases are reported, which occurred among more than 3,000 patients suffering from tuberculosis. Thus, the frequency was slightly more than 0.2 per cent. The condition was observed only in youthful patients. Only one resection specimen is described in a few words; the morphology of the focus appears to correspond with that observed in the cases of the present writers.

OBSERVATIONS

At Berg en Bosch a number of cases of *type II*, reactivations of the primary pulmonary focus, have been collected. The rarity of this finding is demonstrated by the following figures. Between January 1, 1950, and September 1, 1957, a total of 4,554 tuberculous patients were discharged from Berg en Bosch. Among them were 12 patients suffering from a local reactivation of an already subsided pulmonary focus; thus, the frequency was about 0.25 per cent.

In arranging the patients into groups of adults and children (in accordance with the system of registration used at Berg en Bosch the age limit for children was fixed at fifteen years), it is shown that the condition was more frequent in children than in adults. Among 1,177 children, a reactivation of the primary focus was found in 7 patients, i.e., in approximately 0.6 per cent. Among 3,377 adults, such a local reactivation occurred in 5 patients which constitutes a

[1] From the Sanatorium "Berg en Bosch," Bilthoven, The Netherlands.

frequency of about 0.15 per cent. This definite predilection for youthful patients is even more distinct if one takes into account the age of the patients who were regarded as adults. These 5 patients were fifteen, sixteen, sixteen, twenty-four, and twenty-seven years of age, respectively.

Thus, the impression is given that local reactivations usually develop in the first few years after subsidence of the primary complex. The clinical data also suggest this. The period between the detection of an active primary complex and the diagnosis of its reactivation was established in 8 patients. It varied between two years and a little more than four years, with an average of more than three and a quarter years. From the discovery of a calcified primary complex until its reactivation in 4 patients, periods of one, three, five, and ten years, respectively, elapsed. All this is in agreement with the experience that, in general, the risk of reactivation of tuberculous processes is reduced with increasing age of the lesions. Nevertheless, some reserve is necessary when drawing a conclusion, because, especially in adults, a greater chance exists that a local reactivation of a primary focus will not always be definitely recognizable as such. This risk is present in cases in which a solitary focus is localized in the apicodorsal areas of the upper lobes or the apical areas of the lower lobes, since postprimary processes are frequently localized in these regions. Therefore, in such cases it is often not clear whether a solitary focus has to be considered as a reactivated primary focus or as a postprimary focus.

Whether (and, if so, to what extent) the patient's age may be of significance for the development of local reactivations cannot be said.

Apart from the 12 cases mentioned above, the present writers now have under observation a 14-year-old girl suffering from the same condition; thus, a total of 13 instances were studied. Some cases in which the diagnosis remained doubtful were excluded from consideration. In 12 cases a certain diagnosis could be made based on accurate data: in 8 patients the primary complex in its active stage had been perpetuated on chest films; and in 4 patients the presence of a partly calcified primary complex which had subsided before the onset of the present disease could be demonstrated from the roentgenograms. In the remaining case the diagnosis was justified on the ground of a probability bordering on certainty.[2]

Clinical findings: The clinical data from the present cases are presented in brief outline at this point, and certain illustrative cases are presented later in this article.

There were 8 male and 5 female patients. At the time of detection the oldest patient was twenty-seven, the youngest nine years old. Complaints and symptoms noted were: hemoptysis, high temperature accompanied by a definite general malaise, cough, expectoration, fatigue, weakness, and loss of weight. An acceleration of the erythrocyte sedimentation rate and alterations in the differential count of the leukocytes were also observed. Some of the symptoms mentioned were usually present, but all were not necessarily present in every

[2] In a boy sixteen years old, who became acutely ill, a solitary excavated caseous focus was found. This focus, containing large calcified spots, was situated in the anterobasal segment of the left lower lobe; the left hilar lymph nodes also contained calcium.

patient. The discharge of *M. tuberculosis* in the sputum was demonstrated almost without exception. In accordance with the nature and the extent of the liquefaction in the focus, the number of tubercle bacilli in the sputum varied from large numbers seen on microscopy to an occasional one obtained only by culture.

Finally, it should be noted that the problem of the causes of reactivation was in no case elucidated to any degree by either the history or the clinical data.

Roentgenographic findings: The roentgenographic findings were more interesting than the clinical ones. The fairly voluminous foci were usually sharply demarcated from the surrounding lung tissue. The size varied from that of a cherry to that of a chestnut, but one focus was as large as a hen's egg with a hazy border. In another case, the liquefaction and the excavation had advanced to such an extent that the hazily delimited lesion, the size of a plum, finally assumed the appearance of a classic thin-walled cavity. At that time, microscopy of the sputum revealed large numbers of tubercule bacilli. Nearly all of the foci (eleven of thirteen) contained calcium, which was localized eccentrically. All foci but one contained a cavity. Except for the case mentioned, the cavity was always fairly small as compared with the size of the focus itself; a striking feature was the eccentric position of the cavity which was invariably situated opposite the calcium deposits.

It is of significance that the local extension was always accompanied by disseminations in the lung tissue. In the majority of cases, these were limited to a number of small foci in the immediate surroundings of the large focus. In 4 patients, however, a multitude of small foci occupied a larger area, in every case in the homolateral lung. The aspect and the localization (situated peripherally in the lung tissue, in the middle lobe, and in the basal segments of the lower lobes) were exactly the same as those of the classic bronchogenic disseminations in cavitary pulmonary tuberculosis. In this connection, it should be observed that, in addition to this series of verified cases, some cases of probably the same nature were observed in which the focus behaved entirely like a classic highly active cavity. A severe clinical condition was accompanied by expectoration of large numbers of tubercle bacilli in the sputum, which was sometimes blood-stained. This occurred in association with the development of extensive bronchogenic disseminations in both lungs.

In 4 patients, no remnants of the original lymph node component of the primary complex were traceable on the roentgenograms. In 8 patients, calcifications were clearly visible in the homolateral hilus and, in one patient, also in the contralateral hilus. A simultaneous reactivation in the lymph node focus was not demonstrable either in the roentgenograms or on bronchoscopy.

Localization of the foci: With respect to localization of the foci, nine were localized subpleurally: eight foci were in the right and five in the left lung. The distribution in the lobes was: three foci in the upper lobes (except the lingula), one of which was in the pectoral segment; three foci in the apex of the lower lobe; one focus in the lingula; and six foci in the basal segments of the lower lobes.

It is not possible to answer the question whether a certain localization of the

primary focus may predispose to the development of a local recurrence. Because of the small number of cases, a comparison with the localization of primary pulmonary foci in general would be meaningless.

Course of the reactivated focus: The course of the reactivated focus is also significant. The treatment was conservative in only 2 cases. In one case the excavated and partly calcified focus, the size of a cherry, changed within a few months into a scar the size of a grain of wheat which still contained an occasional calcified spot. Tubercle bacilli disappeared from the sputum, and the patient is in an excellent condition at this moment (five years after her discharge from the hospital). The scar is barely demonstrable roentgenographically. In the second patient, a resection could not be considered because of diffuse bronchogenic dissemination. The excavated focus, once the size of a plum, diminished to the size of a cherry. Observation, which has now lasted for five months, is being continued.

Among the 11 patients who were operated upon, there were 2 cases in which the foci had changed into a scar. In the remaining 9 cases the observation period from the discovery until a resection was performed ranged from 2 months up to two and a half years. In none of these cases did the reactivated focus show a tendency to improve. Regressions of the process as seen on the chest films occurred, if at all, only in the disseminated foci.

In all cases, pulmonary resection[3] was well tolerated. Occasionally, the procedure was technically difficult because of the many adhesions between the hilar vessels and bronchi, resulting from the preceding tuberculous inflammation in the regional lymph nodes.

The postoperative course was uneventful in every case and a satisfactory re-expansion was obtained. After discharge from the sanatorium, all of the patients have remained in excellent condition.

Histopathologic studies of resected foci: Pulmonary resection provided an opportunity to study the morphology of the foci in 11 cases. Six of the foci had not undergone changes of any significance since their discovery, as shown by the chest films. These foci were found to have essential characteristics in common. They were all caseous foci. Examination always clearly showed that they were composed of a small, unmistakably older portion and a larger, more recent area. The older part invariably consisted of a largely calcified caseous focus, which also contained numerous cholesterol crystals, a phenomenon which is also evidence of the existence of the focus for a long period. This older area was always eccentrically localized and was situated immediately against the capsule surrounding the entire focus. At that site the capsule consisted of connective tissue without any trace of structures typical of tuberculosis. This older caseous area was embedded in the main mass of the focus, which obviously had become caseous more recently. With the aid of van Gieson's stain, a broad zone of collagenous fibers was always found which separated the older from the more recent caseous mass. It may be assumed with a high degree of probability that the older area should be regarded as the original primary focus. The remainder

[3] All of the operations were performed by Dr. M. C. A. Klinkenbergh.

of the focus should be considered as the extension. This assumption was confirmed by the study of the roentgenograms.

The structure of the capsule around the more recent part of the focus was clearly different from that surrounding the old primary focus. The connective tissue here had a finer structure and contained a considerable number of lymphocytes and plasma cells. The most striking feature was the presence of a zone of tuberculous granulation tissue between the caseous substance and the capsule. In other words, the marginal area in this part showed an active tuberculous inflammation.

The structure of the recent caseous substance was of particular interest. Macroscopic examination revealed a stratified structure. At some distance from each other, numerous narrow, dark-colored lines were visible in the light-colored caseous mass. They ran parallel to each other and approximately parallel to the outer surface of the old primary focus. From the sections, it became clear that these lines corresponded with layers of collagenous connective tissue. These demarcated sectors of necrotic tissue differed from each other in the degree to which the original pattern of the pre-existent elastic fibres had been preserved in the necrotic tissue. The structure becomes comprehensible by assuming that the local extension, originating from the old focus, took place in successive steps.

It can be stated that, in the writers' experience, the local reactivation of the primary focus sometimes takes place in a manner typical of tuberculomas (2–4). In such cases the result may also be regarded as a tuberculoma. This means that the final size of the focus is not reached in one, but in several phases. In a few cases, it was possible to observe such an extension in phases on the chest roentgenograms. The extension appears to develop nearly always in an eccentric direction and toward the hilums. The liquefaction, and consequently the excavation thus produced, is nearly always visible on the roentgenogram. In the sections, the excavations are always found in the relatively recent part of the focus. At the place where the cavity borders directly upon the capsule, the latter is lined with tuberculous granulation tissue, sometimes with considerable vascularization. Accordingly, the sputum in such cases contains large numbers of tubercle bacilli. The old primary focus only becomes involved in the liquefaction at a later moment. *Mycobacterium tuberculosis*, which was nearly always demonstrable in the sections, was exclusively found in the recent area of the focus. No special significance can be attached to this finding since, in histologic preparations, the bacteria are very rarely observed at places other than in liquefied caseum. In 3 cases, the caseous material of the focus was cultured for tubercle bacilli before fixation. In all 3 cases the cultures were positive, from which it becomes clear that, in these cases at least, the tubercle bacilli present were viable.

In the foci not yet described so far, the liquefaction and excavation at the time of operation were so far advanced that nothing could be said with certainty about the original structure. Two were changed into fibrotic scars; the same was true of a third focus, but this still showed a few calcified remnants in a small central residual cavity. In the remaining foci, the process of liquefaction and expulsion of the liquefied mass was also in an advanced stage. One focus still

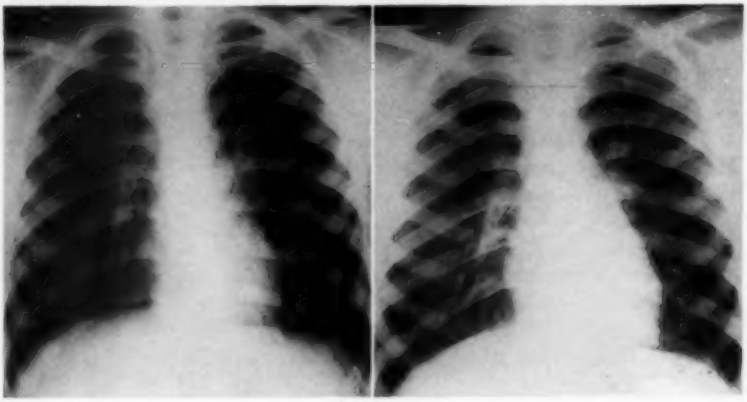
possessed the aspect of a thin-walled cavity with a thin layer of caseum covering the wall. The last focus had completely changed into a pulpy liquefied mass.

Usually a direct communication exists between the cavity and a large-caliber bronchus. In the same way as in an excavated tuberculoma and in a tuberculous cavity, the wall of this bronchus shows tuberculous inflammation. At a distance of a few centimeters from the focus, the mucosa usually is swollen, edematous, and highly infiltrated with lymphocytes and plasma cells. These phenomena become more marked toward the focus. Typical tubercles are seen in the tunica propria. In the last few millimeters before the focus, the epithelium becomes metaplastic and finally disappears either partially or entirely. With this local ulceration, the picture of the draining bronchus is complete.

Illustrative Cases

Case 1. B. V., male, was born in January, 1942. In April, 1952, the patient developed erythema nodosum. Subsequently, a tuberculous primary complex was found in the right lung. The primary focus was localized in the axillary part of the pectoral segment of the right upper lobe (figure 1). From May 3, 1952, until March 22, 1953, the boy was treated in a sanatorium. The lymph-node swelling in the right hilus disappeared and the primary focus calcified rapidly. After his discharge from the sanatorium, the boy was examined every six months. The calcified focus in the right upper lobe remained unchanged (figure 2, roentgenogram of December 7, 1955). In the beginning of 1957, the boy grew thinner and started to cough. Roentgenography revealed a local extension, and the patient was admitted to Berg en Bosch. The boy was then in good condition. There were no general evolutive phenomena. He did not cough, but a few cultures of gastric washings were positive for tubercle bacilli.

Roentgenographic examination (figure 3). The right hilus contained calcified remainders of the lymph-node foci of the primary complex. In the axillary area of the pectoral segment of the right upper lobe there was a cavitary caseous focus the size of a chestnut, which, apart



Case 1

FIG. 1. (Left) Roentgenogram obtained April 4, 1952. Swollen lymph nodes in the right hilus. Small focus in the right upper lobe.

FIG. 2. (Right) Roentgenogram obtained December 7, 1955. Calcified focus in the right upper lobe.

FIG. 3. Tomogram of April 8, 1957. Small calcified focus, embedded in a larger sharply delimited focus, containing a slitlike cavity at the side of the hilus. Calcified spots in the hilus.

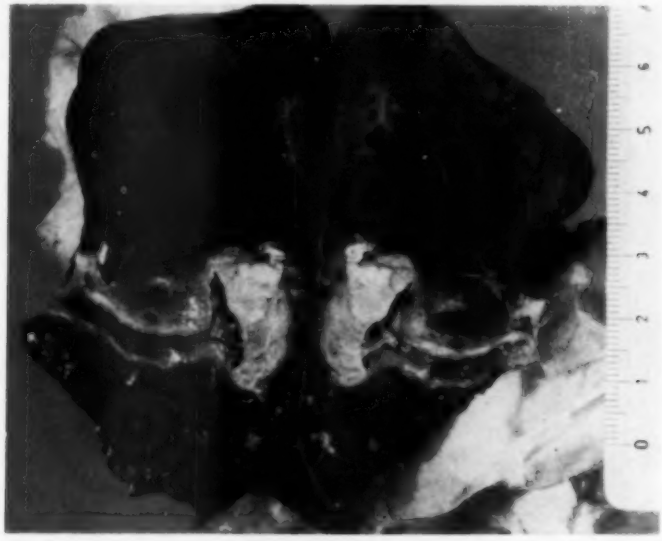
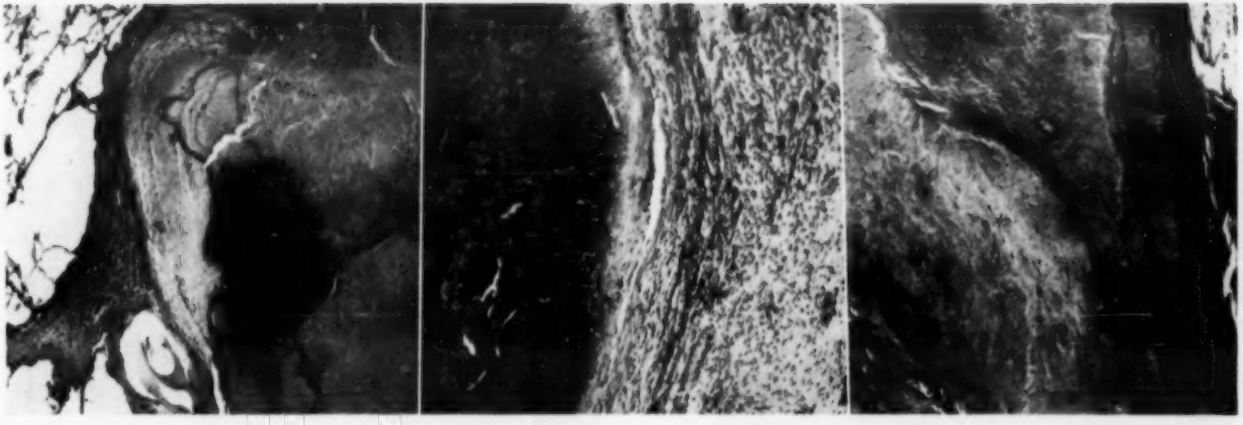


FIG. 4. *Case 1*. Specimen (scale in centimeters). The focus is seen to consist of a calcified focus, embedded in a larger caseous focus, having a laminated structure. The axillary branch of the pectoral bronchus, which opens into a slitlike cavity, has a thickened wall. In the vicinity of the focus, disseminated small foci may be seen.



Case 1

FIG. 5. (Left) Connective tissue capsule surrounding the calcified part of the focus. (Stain: hemotoxylin-azophloxin; magnification 15 ×)

FIG. 6. (Center) Connective tissue capsule surrounding the calcified part of the focus. (Stain: hemotoxylin-azophloxin; magnification 60 ×)

FIG. 7. (Right) Structure of the more recently formed part of the focus. Zones of collagenous fibers (seen as dark tracts in the photograph) comprise sectors of caseum, differing in the degree to which the original pattern of the pre-existent elastic fibers are preserved. (Stains: Weigert's elastica and van Gieson's; magnification, 60 ×)

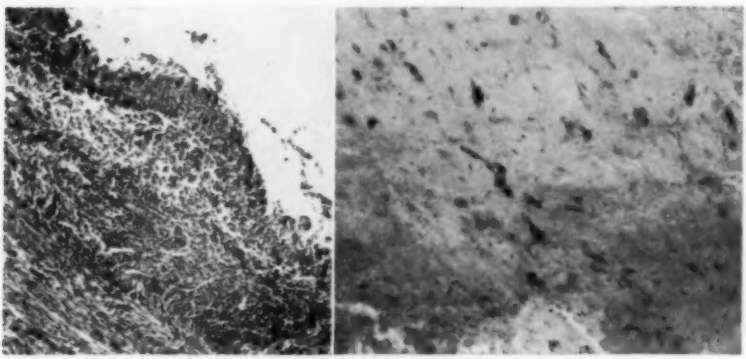
from a small cavity, also contained a calcified part. Somewhat lower in the same subsegment there was a group of small foci.

Operation: Since some of the small foci were situated in the dorsal segment, it was decided to perform a lobectomy. Resection of the upper lobe, which was difficult due to marked adhesions between the blood vessels and bronchi in the hilus, was carried out without complications.

Pathologic anatomy:

Macroscopic examination (figure 4): The axillary subsegment of the pectoral segment contained a sharply delimited caseous focus the size of a plum, with a slitlike cavity at the side of the hilus. The axillary subsegmental branch of the pectoral bronchus opened into this cavity. In the lateral superior part of the focus a sharply demarcated area existed, which was clearly lighter in color and of a more firm consistency than the rest of the focus. The large focus showed a distinctly stratified structure. In the caseous mass, narrow, dark lines were visible in the caseous substance at some distance from each other; the lines ran parallel to each other and to the outer surface of the white focus. Distally, the draining bronchus was somewhat narrowed concentrically, due particularly to an increase of peribronchial tissue. The mucous membrane was slightly swollen. Likewise, in the pectoral segment, but lower, a group of small foci about the size of a pinhead was present.

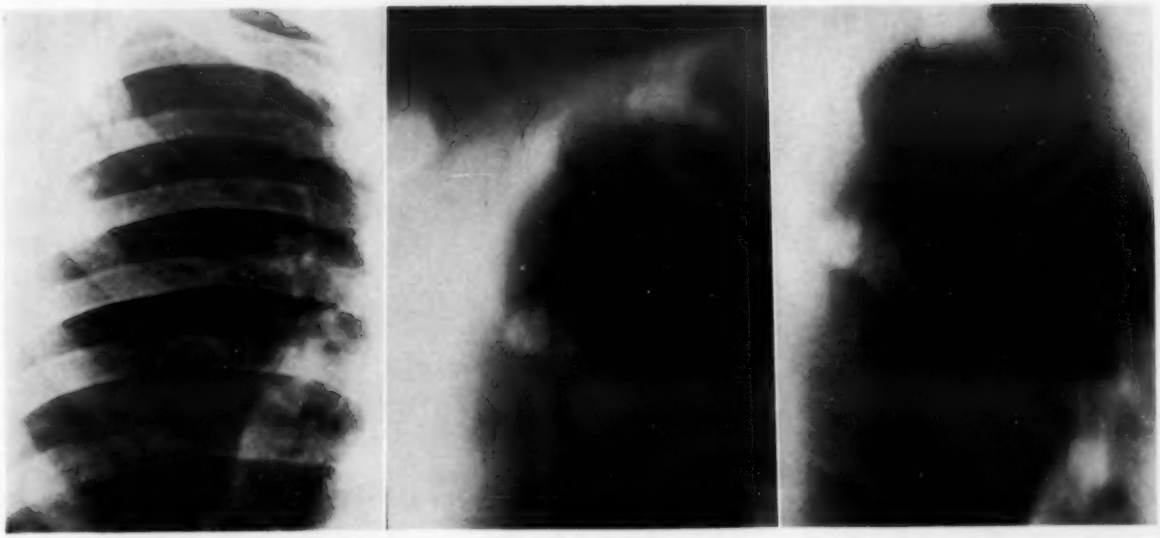
Microscopic examination: The eccentric light-colored part of the focus consisted of a highly calcified caseous mass surrounded by a collagenous connective tissue capsule (figures 5 and 6). Sections stained according to van Gieson's method showed that at the borderline between the calcified mass and the large noncalcified caseous mass, in which the former was embedded, this connective tissue layer also was present. The latter part of the focus showed a distinctly stratified structure, attributable to the presence of layers of collagenous connective tissue (figure 7). The sections of the caseous mass comprised by these layers differed from each other in the degree to which the original pattern of the pre-existent elastic fibers had been preserved. This part of the focus was surrounded as well by a connective tissue capsule which, however, contained more nuclei than the capsule surrounding the calcified area. Furthermore, between the connective tissue and the caseum, a layer of specific granulation tissue was present. This layer proceeded around the slitlike cavity



Case 1

FIG. 8. (Left) Above the cavity the capsule is covered by specific granulation tissue. (Stain: hemotoxylin-azophloxin; magnification 60 ×)

FIG. 9. (Right) Numerous acid-fast bacilli in the recent part of the focus. (Stain: Schmorl's modification of Ziehl-Neelsen's; magnification ± 100 ×)



Case 2

FIG. 10. (Left) Roentgenogram of December 1, 1952. Small calcified focus in the right upper lobe.

FIG. 11. (Center) Tomogram of May 16, 1955. At the medial side of the calcified focus a more recently formed and less dense extension may be seen.

FIG. 12. (Right) Tomogram of June 28, 1955. Since the last tomogram (figure 11) still another extension has developed toward the hilus.

(figure 8) to as far as the opening of the draining bronchus. The cavity contained small remnants of liquefied caseum. In the noncalcified caseous mass, especially in the neighborhood of the cavity, acid-fast bacilli were observed in large numbers (figure 9).

The draining bronchus showed specific granulations which were, at least partially, lined with stratified epithelium. These alterations became more extensive as well as more intensive toward the focus. In the most distal part of the bronchus, the mucous membrane showed local ulcerations.

Comment: A primary tuberculous pulmonary focus subsided and became calcified in a fairly rapid manner. The focus thereafter remained unchanged for about four years. Then a local reactivation developed. In the specimen, the calcified primary focus, surrounded by a collagenous connective tissue capsule, was found again, embedded laterally in the newly formed focus. The latter possessed a stratified structure, suggesting that it had developed in stages. The apparently more recently formed caseum contained numerous tubercle bacilli, which was especially true for the environment of the cavity. The capsule surrounding the newly formed part of the focus was obviously still in an active stage of tuberculous inflammation. Furthermore, the draining bronchus showed a locally ulcerative, tuberculous inflammation.

Case 2. A. E., female, was born in January, 1941.

Clinical data: As early as 1945, this patient had a positive tuberculin reaction. At fluoroscopy a calcified focus was detected, localized subpleurally in the axillary region of the right upper lobe. During a regular follow-up examination, no change in the chest film was observed (figure 10; roentgenogram of December 1, 1952). At a routine examination in May, 1955, a local extension was observed (figure 11, planigrams of May 16, 1955). Awaiting her admission to the sanatorium, the patient was kept on strict bed rest. Six weeks afterward she was admitted to Berg en Bosch. She was in excellent condition. There were no general

FIG. 13. *Case 2.* Specimen in which the tuberculous process is clearly seen to consist of three different parts, of which the most lateral calcified portion has existed for at least ten years, the middle noncalcified caseous portion for about one year, and the most medial one for eight weeks at the most.

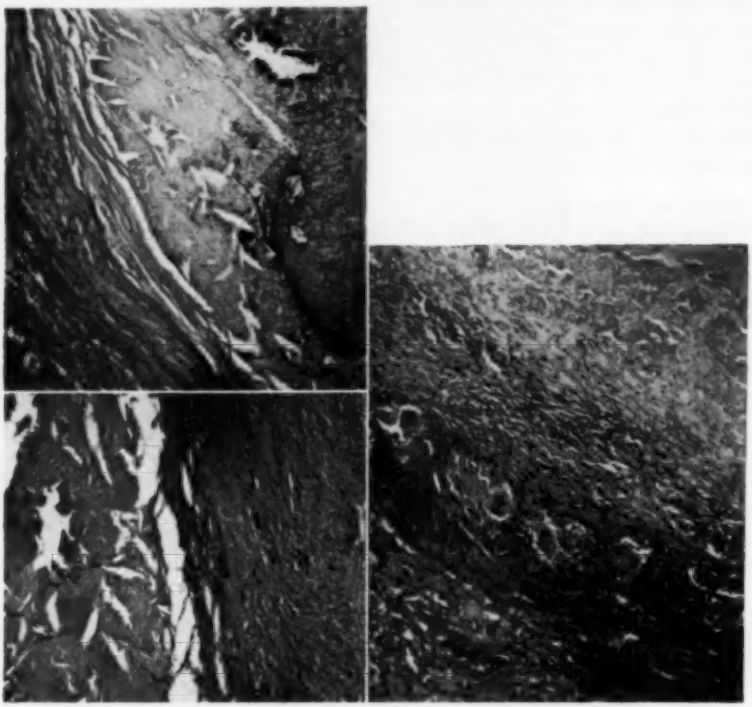
evolutive symptoms. She did not expectorate, but a guinea pig test of the gastric washings was positive for tubercle bacilli.

Roentgenographic examination: The old calcified focus and the original local extension were unchanged at the time of admission to the hospital. However, still another extension had developed toward the hilus (figure 12, planigrams of June 28, 1955). This latter extension was, therefore, of no more than six weeks' standing.

Operation: The axillary subsegment of the dorsal segment of the right upper lobe was removed without difficulty.

Pathologic anatomy:

Macroscopic examination (figure 13): An oblong pathologic process was found, clearly composed of three different sections. The lateral part was a calcified caseous focus sur-

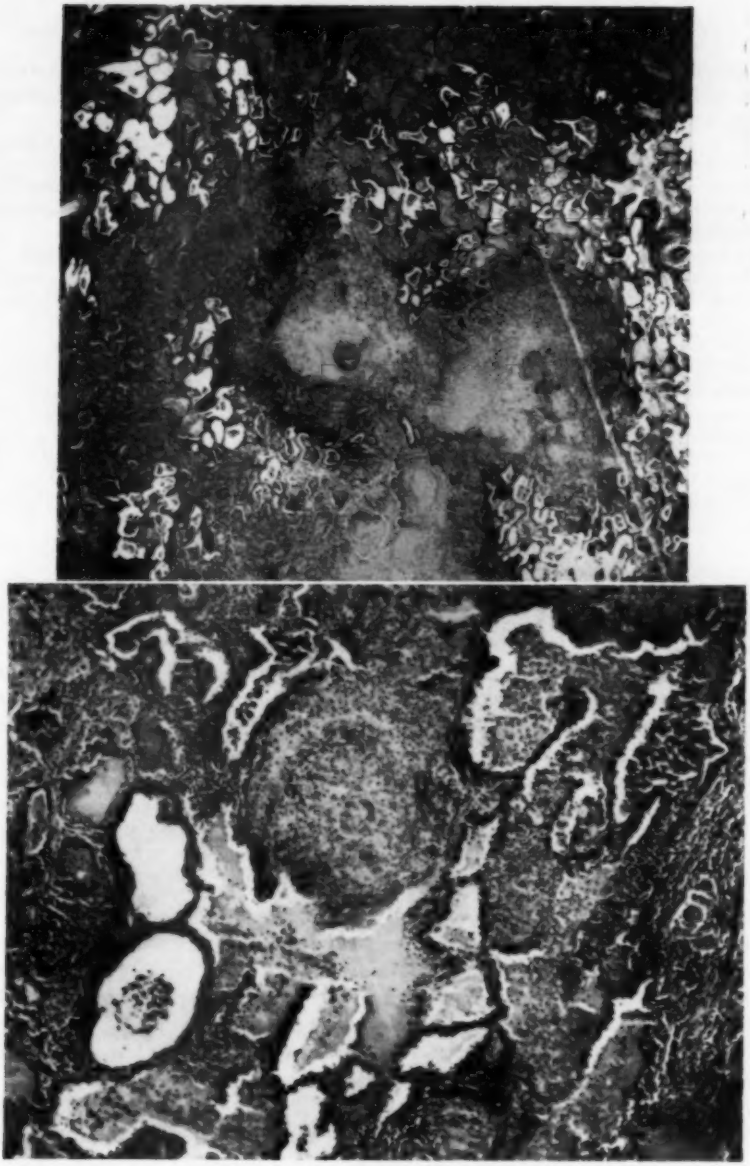


Case 2

FIG. 14. (Upper left). Collagenous capsule surrounding the calcified focus. The inner zone of the capsule is hyalinized. Note the clefts in the caseum left by cholesterol crystals. (Stain: hemotoxylin-azophloxin; magnification 60 ×)

FIG. 15. (Lower left) A strip of collagenous tissue between the calcified part at the left and the noncalcified part at the right is seen as a darker zone in the middle of the photograph. (Stain: Weigert's elastica and van Gieson's; magnification 60 ×)

FIG. 16. (Right) Specific granulation tissue in the capsule, surrounding the noncalcified caseous middle part of the focus. (Stain: hemotoxylin-azophloxin; magnification 60 ×)



Case 2

FIG. 17. (Upper) Structure of the most recent part of the focus. (Stain: hemotoxylin-azophloxin; magnification 15 ×)

FIG. 18. (Lower) Exudative and productive lesions in the fresh part of the focus. (Stain: hemotoxylin-azophloxin; magnification 60 ×)

rounded by a capsule. Directly against this, at the medial side, was a crescent-shaped caseous noncalcified mass, which also was encapsulated. The third section, facing the hilus, consisted of a nonaerated zone of grayish pulmonary tissue of firm consistency.

Microscopy: On microscopy, the subpleural part was also found to consist of a highly calcified caseous mass, showing numerous small clefts, which obviously had contained cholesterol crystals. Scattered remnants of the pre-existent elastic fibers were also found. This part of the process was surrounded by a collagenous connective tissue capsule bordering immediately on the caseous substance (figure 14).

Between the calcified part and the caseous middle section of the process, this capsule, or at least a remnant of it, was still demonstrable in the sections stained by van Giesons's method (figure 15). The latter middle zone showed the original pattern of the elastic fibers to be fairly well preserved. Small clefts left by cholesterol crystals were absent. The connective tissue capsule was richer in cells and poorer in collagenous fibers than in the area already described. Furthermore, a layer of specific granulation tissue was present between the caseous substance and the capsule (figure 16). The most centrally localized part of the process obviously was composed of lung tissue in a state of active inflammation. Scattered throughout this area were found irregularly shaped and only partly encapsulated caseous foci and smaller foci composed of tuberculous granulation tissue. The pulmonary tissue in between these foci showed interstitial fibrosis together with swelling of the septal cells in many places. Many alveoli were filled with a protein-rich fluid in which numerous macrophages and a few lymphocytes were found (figures 17, 18).

Acid-fast bacilli were not found in the sections, but *M. tuberculosis* was cultivated from the noncalcified caseous substance.

Comment: From a calcified primary focus, remaining quiet and unchanged for a long time (at least ten years), a local extension developed which, according to the roentgenographic findings, was brought about gradually. The original focus was found to be a largely calcified mass of caseum surrounded by a collagenous connective tissue capsule. The section formed at the first phase of extension, existing no longer than one year, proved to be a rather fresh caseous focus from which *M. tuberculosis* could be cultured. This mass was surrounded by a rather thin granulating capsule. The most recently formed part of the focus, present for at least eight weeks, appeared to be a zone of active pneumonia in which caseation was going on.

Summary

Local reactivation of the subsided primary focus is a rare phenomenon which the writers have observed only in youthful patients and especially in children.

Both the clinical and the roentgenographic pictures correspond with that which a liquefying caseous focus may show in general. Its course may be fulminant, thus assuming all characteristics of a cavitary tuberculosis. Through extensive liquefaction and expulsion of the liquefied caseous mass, the focus may be transformed into a scar.

The morphology sometimes clearly demonstrates that there has been an extension around an old calcified focus. This extension evidently has taken place in successive stages, sometimes in exactly the same manner in which a pulmonary tuberculoma is supposed to develop. The liquefaction appears in the relatively recent part of the focus. There too were found the tubercle bacilli, which virtually were always present. It has been established, at least in some cases, that these bacilli were viable.

No explanations for the initiation of the extension were found. Because of the liquefaction, which is present almost without exception and especially because of the tendency to periodic progression, the writers always regard local reactivation of an initially subsided primary tuberculous pulmonary focus as an indication for a pulmonary resection.

Sumario

Reactivación Local del Foco Tuberculoso Primario en el Pulmón

La reactivación local del foco primario sosegado es un fenómeno raro, que los AA. no han observado más que en los enfermos jóvenes y en particular en los niños.

El cuadro tanto clínico como radiográfico corresponde a lo que un foco caseoso en vías de licuación suele revelar en general. La evolución puede ser fulminante, revistiendo así todas las características de una tuberculosis cavitaria. Por medio de extensa licuación y expulsión de la masa caseosa licuada el foco puede transformarse en cicatriz.

La morfología muestra algunas veces claramente que ha habbido difusión alrededor de un foco antiguo calcificado. Esta difusión ha tenido lugar evidentemente en etapas sucesivas, algunas veces precisamente del mismo modo en que se supone se forma un tuberculoma pulmonar. También se encontraron allí los bacilos tuberculosos que virtualmente estaban siempre presentes. Se ha establecido, a lo menos en algunos casos, que estos bacilos eran viables.

No se descubrieron explicaciones de la iniciación de la difusión. Debido a la licuación, que existe casi sin excepción y en particular debido a la tendencia a la agravación periódica, los AA. consideran siempre la reactivación local de un foco tuberculoso primario del pulmón, apaciguado antes, como indicación para una resección pulmonar.

Resume

Réactivation locale du foyer pulmonaire de primoinfection

La réactivation locale d'un foyer de primoinfection stabilisé est un phénomène rare, que les auteurs n'ont observé que chez des malades jeunes et surtout chez l'enfant.

L'image clinique et radiologique correspondent toutes deux à celle qu'on observe en général dans le foyer caséeux ramolli. Son évolution peut être foudroyante, ayant alors tous les caractères d'une tuberculose cavitaire. La cicatrisation du foyer peut se manifester après ramollissement étendu et évacuation de la masse caséeuse.

L'image montre parfois clairement l'extension persistant autour d'un ancien foyer calcifié. Cette extension du foyer, évidente, s'est faite par étapes successives, parfois exactement de la même manière que l'évolution classique d'un tuberculome pulmonaire. C'est au niveau de la partie la plus récente du foyer que cette fonte caséeuse apparaît. C'est également là que l'on a trouvé des bacilles tuberculeux, toujours virtuellement présents. Il a été établi, du moins dans quelques cas, que ces bacilles étaient vivants.

Il n'a été obtenu aucune explication quant à l'origine de cette extension du foyer. En raison du ramollissement, presque toujours présent, et en particulier à cause de la tendance à l'extension periodique, les auteurs considèrent toujours la réactivation locale d'un foyer pulmonaire de primoinfection initialement stabilisé comme une des indications de la résection pulmonaire.

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PREGNANCY AFTER PNEUMONECTOMY FOR PULMONARY TUBERCULOSIS[1]

Analysis of a Collected Series of Seventy-four Pregnancies in the Netherlands

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Introduction

Little is known about the course of pregnancy in patients who have undergone pneumonectomy for pulmonary tuberculosis, and there is little detailed knowledge of their labor and puerperium. Young female pneumonectomy patients often ask their physicians: "Is it sensible to marry and is there any objection to having children?" To obtain some insight into this problem a national investigation was set up in the Netherlands (1), and certain of the findings form the basis of the present report.

Review of Literature

Much has been published about the risk of pregnancy in women suffering from tuberculosis (2–12). Friedman's statement (5) adequately expresses the opinion of most of the writers: "Pregnancy probably exerts little or no influence on the incidence or course of tuberculosis."

Gaensler and associates (13) observed the course of 9 pregnancies in 7 patients with diminished pulmonary function.[2] Two of the patients had undergone pneumonectomies for pulmonary tuberculosis; one had a homolateral and one a heterolateral thoracoplasty. In contrast to normal subjects, the patients with moderately disturbed pulmonary function did not complain of dyspnea at any time during pregnancy. Patients with severely impaired function were not more disabled during pregnancy than before. The writers concluded: "Patients with restrictive respiratory insufficiency, who are not dyspneic at rest, should tolerate pregnancy without great difficulty."

Folsome and Kuntze (14) reported 20 pregnancies in 14 patients who had pneumonectomies for tuberculosis. In 2 patients the lung was removed during pregnancy. In the remaining 12 patients, of whom 8 were primigravidae, there were 2 spontaneous abortions, 4 therapeutic abortions, 3 premature births, and 11 term births. Seven of the deliveries were spontaneous, 5 were forceps deliveries, 3 were cesarean sections, and one was a cesarean hysterectomy for rupture of a previous section scar. In all cases labor was terminated within twenty-four hours. The writers concluded that pulmonary tuberculosis treated with major surgery did not threaten pregnancy. They found no essential differences between the medically treated patients and those who underwent major thoracic surgery; there were no indications for therapeutic abortion. The writers stated: "Dyspnea during pregnancy or labor was not a factor in any of our cases."

Thomson and Bressler (15) reported a pneumonectomy for unilateral tuberculosis in the twenty-fourth week of pregnancy. Delivery at the thirty-fifth week was accomplished by low forceps after eight and one-half hours of labor.

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[2] These observations constitute part of a study of pulmonary function in pregnancy.

Corner and Nesbitt (16) gave details of 15 cases of pregnancy after pulmonary resection which included 4 pneumonectomy patients, 2 of whom had an eight-rib thoracoplasty. They found that the irreparable loss of the vital capacity was compensated for by more rapid and more regular breathing and by decreased resistance of the respiratory passages during pregnancy. This, they supposed, probably accounts for the fact that subjective dyspnea is more common in normal pregnant patients than in those with pulmonary insufficiency. It is noteworthy that in one of their cases the vital capacity was only 900 ml. (30 per cent of the normal value). Delivery was spontaneous and without complications. The writers draw the following conclusions from the study of their cases:

1. Pneumonectomy and pulmonary resection are not contraindications to pregnancy, provided the patient is not dyspneic at rest or on slight exertion.
2. Patients with pulmonary resection who are not dyspneic under normal conditions go through labor and vaginal delivery without difficulty.
3. Pneumonectomy and lobectomy may be performed during pregnancy with safety to mother and child, if necessary to the welfare of the mother.
4. Because of their reduced respiratory reserve, pregnant patients undergoing pneumonectomy must be protected from any illness which will tend to reduce this limited reserve.

Bérard and associates (17) mentioned that in their series of 350 pneumonectomy patients, 9 of the 270 who were successfully treated passed through one or more pregnancies.

Reading the literature, the experience of the course of pregnancy in pneumonectomy patients is generally favorable. The same may be said of the labor and puerperium of these patients. The published series, however, are too small to enable one to draw conclusions.

Observations

Frequency and Course of Pregnancy in Patients after Pneumonectomy for Pulmonary Tuberculosis in the Netherlands

Information was received concerning 64 patients who passed through 74 pregnancies after pneumonectomies for pulmonary tuberculosis. Thirty of these patients were single at the time of resection. Indications for operation are presented in table 1.

TABLE 1

Indications for Operation in Sixty-Four Female Patients Who Underwent Pneumonectomy for Pulmonary Tuberculosis

Number of Patients	Indication for Pneumonectomy
17	Destroyed lung
27	Unilateral extensive cavernous process
3	Stenosis of the main bronchus
5	Empyema (one with a bronchial fistula)
3	Small process (complication during the operation made pneumonectomy necessary)
9	No indication mentioned

In 42 patients the left lung was removed, in 20 the right lung, while in 2 patients the side on which the operation was performed was not indicated.

In 48 patients the sputum was positive for tubercle bacilli on microscopy or culture until the operation date. There were only 3 patients with sputum negative for tubercle bacilli; the indications for surgery in these cases were stenosis of the main bronchus in 2, and empyema without bronchial fistula in the third case. In 11 cases no information was given about tubercle bacilli in the sputum before the resection.

Fifty-six of the 64 patients underwent pneumonectomy without thoracoplasty. Fifteen had an elevated paradoxically moving diaphragm on the side of the operation. Five had a prosthesis of plastic balls; in 3 of these patients the diaphragm on the operated side was paralyzed. Ten others showed a substantial mediastinal "hernia" of the remaining lung into the empty thoracic cage; in 4 patients there was scoliosis. In 6 patients a thoracoplasty was performed at an unspecified time during the course of the disease; eight ribs were removed in 5 patients and nine in one; one of these patients had an important degree of scoliosis.

Very incomplete information was received concerning the postoperative pulmonary function. This is due to the fact that 39 of the 64 operations were performed before 1952. Only relative worth can be attached to the pulmonary function investigations which were performed in various hospitals with different apparatus from 1951 to 1956. Nevertheless, they do shed some light on the problem.

The vital capacity was established in 38 patients at various unspecified times after the operation (table 2). In only 11 of the 38 patients was the postoperative vital capacity more than 2,000 ml. In 27 of the 38 patients the vital capacity was equal to or more than the calculated value of the remaining lung. The average of the vital capacity was 1,570 ml. for the 12 remaining left lungs and 1,890 ml. for the 26 remaining right lungs. The lowest vital capacity in a remaining right

TABLE 2

VITAL CAPACITY IN THIRTY-EIGHT FEMALE PATIENTS AT SOME PERIOD AFTER PNEUMONECTOMY

Number of Patients	Vital Capacity	Average Vital Capacity	Average Normal Values			
			Calculated to Length and Age (18)	Group Average	For the Remaining Lung*	Group Average for the Remaining Lung
	ml.	*ml.*	*ml.*	*per cent*	*ml.*	*per cent*
5	1,000–1,300	1,160	3,000	38	1,480	78
8	1,300–1,600	1,490	3,120	48	1,560	96
8	1,600–1,900	1,720	3,080	56	1,560	110
10	1,900–2,200	2,000	3,060	65	1,620	123
7	2,200–2,500	2,380	3,180	75	1,720	138

* This value has been derived from the calculated normal value according to the proportion R:L = 55:45.

TABLE 3

TIME INTERVAL BETWEEN PNEUMONECTOMY AND THE FIRST PARTURITION FOLLOWING OPERATION

Time Interval	Number of Patients	Number of the Pregnancy						
		1	2	3	4	7	8	?
months								
0- 9	2	1		1				
9–18	4		1		1	2		
18–24	6	2	3	1				
24–36	27	18	3	3	1	1	1	
36–48	12	8	2	1				1
48–64	8	7	1					
64–98	4	4						
Unknown	1							1
Total	64	40	10	6	2	3	1	2

lung was 1,120 ml.; this patient was slightly dyspneic on taking moderate exercise. The lowest vital capacity in a remaining left lung, 1,090 ml., was found in a 33-year-old patient who gave birth to her seventh child after the pneumonectomy. One year after the birth she showed no adverse effects.

The *one-second timed* vital capacity was established after the operation in only 28 patients. In 9 patients it was less than 70 per cent of the vital capacity; in 9 it was between 70 and 75 per cent; and in 10 patients it was more than 75 per cent.

In only 19 patients was the postoperative residual volume estimated. It is given as a percentage of the total lung capacity. In 7 patients the residual volume was 18 to 25 per cent of the total capacity; in 9 it was 25 to 36 per cent; and in 3 patients it amounted to more than 36 per cent.

The time interval between pneumonectomy and the first parturition after the operation is given in table 3, and the number of the pregnancy is indicated.

At the time of the investigation, 8 patients twice passed through pregnancy after the operation; a ninth was six months' pregnant. One patient gave birth to a fully-developed but stillborn child three times in succession; in her case there was a rhesus antagonism. In 37 patients the delivery took place at a clinic or infirmary; 12 patients had deliveries at home; of the remaining 25 pregnancies, the only detail given was that the course of the labor was uneventful.

In 70 patients the parturition was spontaneous; in 2 of these the expulsion period was shortened. Forceps were used in only one case. Cesarean section was necessary in 2 cases—in one of them because of a serious dyspnea which resulted from an exudative pleuritis in the last month of the gravidity.

The 74 pregnancies resulted in 70 healthy children; 4 children were stillborn, 3 of whom were children of the same mother. In none of these deaths was there a clear connection with the tuberculosis of the mother.

The following complications arose during pregnancy and puerperium: in the last month of pregnancy one patient developed an exudative pleuritis at the side of the remaining lung. Because of dyspnea, a cesarean section was performed as

the woman was almost at term. In her case the pneumonectomy had been performed in the third month of the pregnancy. At the time of the investigation she had no serious complaints, and the child was healthy. One woman had an atypical pneumonia during the last month of pregnancy and her child was stillborn a month early. This patient was soon dyspneic; she was suffering from a chronic bacterial bronchitis. During the pregnancy in one patient, a bronchial fistula was found which lasted after the parturition. The delivery was uneventful and the child was healthy. In one case a tuberculous empyema was discovered two months after the delivery. Pneumonectomy had been performed more than four years previously; at the same operation a plastic ball prosthesis had been inserted. The empyema was treated with a Schede (19) thoracoplasty, at which time the prosthetic material was removed. The patient suffered no further symptoms after that.

One patient discharged tubercle bacilli in the sputum on one occasion after the parturition; all subsequent cultures were negative. A year afterward, this patient gave birth to her second child.

At the time of re-examination the domestic circumstances of the 64 patients were as follows: 59 patients did their housework with or without assistance and experienced no adverse symptoms. Two patients were severely dyspneic; they were able to do only light housework with assistance, but this also held true before their pregnancy. One patient had a bronchial fistula, but she did her work without undue suffering. One woman had a reactivation a year after the parturition and five years after the pneumonectomy; at the time of the investigation she was still undergoing hospital treatment. One woman died a year after the delivery (three years after operation) as a consequence of an atypical pneumonia.

Summarizing the data relating to the 64 patients who had children after pneumonectomies for pulmonary tuberculosis, it was found that:

> The 74 pregnancies produced healthy children in 70 cases (94.5 per cent). Four children were stillborn (3 of them from the same mother, who had rhesus antagonism). The average vital capacity, established in 38 patients, was 1,890 ml. for a remaining right lung and 1,570 ml. for a remaining left lung. The smallest vital capacity for a remaining right as well as for a remaining left lung was 1,100 ml. None of the patients complained of increasing dyspnea as a result of pregnancy. The labor, and in particular the period of expulsion, were not especially difficult despite the fact that 15 patients had paralyzed diaphragms at the time, while 6 others had had eight-rib thoracoplasties. Seventy patients had normal deliveries. Forty-three patients were more than thirty years of age. In 80 per cent of the cases, parturition took place two years or more after the pneumonectomy. At the time of the examination, 58 of the patients did their housework without serious complaint—59 of the 64 patients had been operated on before 1953. In none of the patients was the pregnancy seriously complicated. In 2 patients the pneumonectomy was performed during pregnancy with good results both for mother and child.

Discussion

On the basis of this investigation it may be concluded that the fact of having only one lung does not appreciably harm the state of health of the expectant mother. Nor was any evidence found that pneumonectomy in the mother had exerted an influence detrimental to the growing fetus.

Although the results on the whole were favorable, it is still difficult to answer the question of whether women who have undergone a pneumonectomy should be dissuaded from having children. The patient commonly asks advice on this question when she is discharged from the sanatorium. An individual opinion is necessary in each case, one which considers both what would be best for the patient from a strictly medical point of view and, in the light of this opinion, what actual advice should be given to the patient. It is important to talk over this question with the husband in order that he may fully realize the state of his wife's health and act in no way prejudicial to it. Moreover, the advice given should be fully communicated to the family physician so that he may be aware of the various considerations involved. It is evident that rigidity in giving advice must be avoided and that the patient's environment and psychologic stability must be taken into account. In this connection, the experience derived from this series of pneumonectomy patients is considered to be of great value. The smaller series already demonstrated that pregnancy and delivery could have a very normal course after a pneumonectomy. This is in complete agreement with the results of the present investigation. With regard to patients leaving the sanatorium after a successful pneumonectomy, it is necessary to judge each case separately in the light of any attendant circumstance. It is undoubtedly advisable in these cases to recommend avoidance of pregnancy for the first two years after the operation. After such a period it will be easier to judge the stability of the tuberculous process, the condition of the remaining lung and the mediastinum, and the adaptability of the patient to the new situation.

In the light of the present experiences, it is believed that it will seldom be necessary to advise against a pregnancy if the condition after the pneumonectomy is stable and if there are no serious symptoms of respiratory and cardiac insufficiency. It is likewise advisable to limit the number of pregnancies after a pneumonectomy because the demands the family makes on the mother may possibly be beyond her physical capacity. It is desirable that these women bring up their children themselves as far as they can, for in doing so they will more easily be able to regain any self-confidence lost during their illness. The manner in which the family physician handles his confidential capacity in such a family will be of decisive importance for the rest of the patient's life.

Summary

A survey has been made of the frequency and course of pregnancy in female patients after pneumonectomy for pulmonary tuberculosis. Inquiry produced data on 64 patients from all parts of the Netherlands who had a total of 74 pregnancies. Generally speaking, no adverse effects of the operation, either for the mother or for the child, were seen during pregnancy and labor.

Sumario

Embarazo Consecutivo a la Neumonectomía por Tuberculosis Pulmonar

En un estudio de la frecuencia y la evolución del embarazo en mujeres neumonectomizdas por tuberculosis pulmonar, la investigación aportó datos para 64 enfermas de todas partes

de Holanda, que habían tenido un total de 74 embarazos. Hablando en general, no se observaron efectos adversos durante la gestación y el parto, ni para la madre ni para el hijo.

Resume

Grossesse après pneumectomie pour tuberculose pulmonaire

L'auteur a étudié la fréquence et l'évolution de la grossesse chez des femmes ayant subi une pneumectomie pour tuberculose pulmonaire. Une enquête a fourni des données relatives à 64 patientes de diverses régions de la Hollande; le nombre total des grossesses était de 74. D'une manière générale, durant la grossesse et le travail il n'a été observé aucun effet nocif résultant de l'intervention ni chez la mère, ni chez l'enfant.

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ANTITUBERCULOUS ACTIVITY OF THIOCARBANIDIN IN VITRO AND IN THE EXPERIMENTAL ANIMAL[1, 2]

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INTRODUCTION

Thiocarbanidin[3] is chemically described as 4-isobutoxy-4′-(2-pyridyl) thiocarbanilide (1) and has been shown to be active against human tubercle bacilli *in vitro* and in the laboratory animal (2, 3). Studies are also being conducted in man (4). It is the purpose of this communication to present data on thiocarbanidin relative to its *in vitro* antituberculous activity, and to demonstrate the emergence of resistant organisms and the therapeutic effect alone and in combination with isoniazid[4] and streptomycin[4] on experimentally induced tuberculosis in the guinea pig. Further experiments indicate the relative efficacy of thiocarbanidin on guinea pig tuberculosis when compared with para-aminosalicylic acid (PAS), the effect of thiocarbanidin on an infection produced with thiocarbanidin-resistant tubercle bacilli, and the result of the drug on a hematogenous infection in rabbits produced with bovine tubercle bacilli.

OBSERVATIONS

Growth Inhibitory Effect in Vitro

Liquid Tween®-albumin medium was used to test the *in vitro* activity of thiocarbanidin against the following strains: (*1*) H37Rv, (*2*) H37Rv resistant to thiosemicarbazone, PAS, and isoniazid, (*3*) four recently isolated strains, and (*4*) four atypical photochromogenic strains of mycobacteria. A stock solution of the drug was prepared to contain 40 mg. per ml. in dimethylacetamide from which serial dilutions in media were made. The inoculum into each tube was 0.1 ml. of a ten-day culture of microorganisms in Tween-albumin medium.

All of the human strains, except the H37Rv resistant to thiosemicarbazone, were resistant to 0.1 γ of thiocarbanidin per ml. and susceptible to 0.5 γ per ml., whereas the photochromogens were resistant to 0.1 to 0.25 γ per ml. and susceptible to 1.0 γ per ml. The H37Rv resistant to thiosemicarbazone was resistant to 50 γ of thiocarbanidin per ml.

[1] From the Trudeau Laboratory of the Trudeau Foundation, Inc., Saranac Lake, New York.

[2] This study was supported in part by a research grant (E36 C11) from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service; and by Parke, Davis & Company, Detroit, Michigan.

[3] The thiocarbanidin was generously supplied by Parke, Davis & Company, Detroit, Michigan.

[4] The streptomycin and isoniazid were kindly supplied by Chas. Pfizer & Co., Brooklyn, New York.

Production of Thiocarbanidin-resistant Microorganisms

A strain of thiocarbanidin-resistant H37Rv microorganisms was produced by serial transfer in Tween-albumin medium containing increased concentrations of the drug. Each transfer was made with 0.1 ml. from the tube containing the highest concentration of thiocarbanidin and showing good growth after fourteen days of incubation. After twelve transfers, growth was obtained in the tube containing 5 γ of the drug per ml.

Effect of Thiocarbanidin, Streptomycin, Isoniazid, Alone and Together, on Experimental Tuberculosis in the Guinea Pig

Sixty guinea pigs, each weighing between 450 and 500 gm., were infected intracardially with 0.2 ml. of a suspension containing 0.1 mg. (dry weight) of the human H37Rv tubercle bacilli. The animals were divided into six groups of 10 each, and therapy was begun immediately. Ten animals acted as controls. The five remaining groups were treated as follows:

Group 1: 25 mg. (50 mg. per kg. per day) of thiocarbanidin by mouth
Group 2: 10 mg. (20 mg. per kg. per day) of streptomycin once daily subcutaneously
Group 3: 5 mg. (10 mg. per kg. per day) of isoniazid once daily subcutaneously
Group 4: 25 and 10 mg. of thiocarbanidin and streptomycin once daily subcutaneously
Group 5: 25 and 5 mg. of thiocarbanidin and isoniazid once daily subcutaneously

Therapy was continued uninterruptedly for 150 days, at which time it was discontinued and the relapse rate was noted in the survivors. The results are recorded in table 1.

From the data in table 1 it may be seen that thiocarbanidin has definite antituberculous activity in the guinea pig. Streptomycin and isoniazid are more active than thiocarbanidin when given alone but, when used in combination with either streptomycin or isoniazid, thiocarbanidin does have a definite additive effect.

TABLE 1

SURVIVAL OF GUINEA PIGS TREATED WITH THIOCARBANIDIN, STREPTOMYCIN, AND ISONIAZID ALONE AND IN COMBINATION

Groups	Number of Animals Alive After 150 Days of Treatment	Average Life of Survivors After Stopping Drug	Survivors at 343rd Day	Average Days of Life	Increase Survival Over Controls
		days			
Controls	0/10	0	0/10	33	
THC* 50 mg/kg/day	5/10	56	0/10	139	4-fold
SM† 20 mg/kg/day	5/10	64	0/10	177	5-fold
INH‡ 10 mg/kg/day	9/10	117	2/10	255	8-fold
THC 50 mg/kg/day SM 20 mg/kg/day	10/10	111	0/10	221	7-fold
THC 50 mg/kg/day INH 10 mg/kg/day	10/10	139	4/10	289	9-fold

* THC—thiocarbanidin.
† SM—streptomycin.
‡ INH—isoniazid.

Effect of Thiocarbanidin on an Infection Produced by Thiocarbanidin-resistant Tubercle Bacilli

Forty guinea pigs, weighing between 450 and 500 gm., were infected intracardially with 0.2 ml. of a suspension containing 0.1 mg. (dry weight) of tubercle bacilli. Twenty were infected with H37Rv thiocarbanidin-susceptible and 20 with H37Rv thiocarbandin-resistant tubercle bacilli (resistant to 5 γ per ml.). Ten of each group were used as nontreated controls and 10 were treated with 25 mg. (50 mg. per kg. per day) of thiocarbanidin by mouth once daily.

The control animals infected with the H37Rv thiocarbanidin-susceptible tubercle bacilli had an average survival of thirty-four days, whereas the animals in the treated groups are all still living and well at ninety days. The control animals infected with thiocarbanidin-resistant organisms had an average survival of forty days, but the treated animals had an average survival of fifty-five days, thus showing that thiocarbanidin had little effect upon an infection produced with thiocarbanidin-resistant tubercle bacilli.

Effect of Thiocarbanidin and PAS on Experimental Tuberculosis in Rabbits

Twenty-one rabbits were infected intravenously in the marginal ear vein with 0.25 ml. of a suspension containing 0.02 mg. (dry weight) of the Ravenel strain of *M. tuberculosis* var. *bovis*. Treatment was started when chest roentgenograms indicated advanced disseminated miliary pulmonary disease, which usually occurred from four to six weeks after infection. Four groups of 3 rabbits each were given thiocarbanidin in gelatin capsule by mouth once daily in doses of 10, 20, 40, and 80 mg. per kg. per day. Three groups of 3 rabbits each were given PAS in the drinking water in doses of 100, 400, and 800 mg. per kg. per day. Water intake was carefully watched to make certain that each animal received the required amount of PAS.

Despite the amount of thiocarbanidin given the rabbits, the pulmonary disease increased, as seen by roentgenogram, during the first two weeks of treatment; then started to regress gradually. This same phenomenon occurs when streptomycin, isoniazid, viomycin, or cycloserine are used in the treatment of miliary tuberculosis in rabbits. Three of the rabbits receiving thiocarbanidin died after three to five days of treatment because their disease was too far advanced at the beginning of therapy. These deaths occurred regardless of the thiocarbanidin dosage. Three had shown roentgenographic evidence of clearing of their pulmonary disease even though they had died early of an intercurrent infection. The 6 remaining rabbits—2 which received 20; 2, 40; and 2, 80 mg. per kg. per day of thiocarbanidin—showed marked roentgenographic clearing of their pulmonary disease. At autopsy, after ninety days of therapy, those animals that had shown marked clearing of the disease on the roentgenogram had a few remaining healing tubercles in their lungs and kidneys. Paralysis was noted in some of the rabbits which was undoubtedly caused by a progressive tuberculous brain lesion upon which the drug had little effect even though marked clearing was noted on the roentgenogram. This same phenomenon was observed in previous experiments in rabbits which were infected intravenously with virulent bovine tubercle bacilli and treated with drugs such as thiosemi-

carbazone and cycloserine. Those animals treated with PAS all succumbed to their disease without showing any roentgenographic improvement of their pulmonary disease.

Effect of Thiocarbanidin and PAS on Experimental Tuberculosis in Guinea Pigs

Eighty-five guinea pigs, each weighing between 450 and 500 gm., were infected subcutaneously with 0.25 ml. of a suspension containing 0.1 mg. (dry weight) of H37Rv microorganisms. Treatment was started twenty-three days after infection, at which time all animals reacted to 5 per cent Old Tuberculin. Therapy was continued for sixty-six days. All survivors were sacrificed 130 days after infection, or 41 days after treatment was discontinued. All animals were given the drug in gelatin capsules by forced feeding once daily. Five guinea pigs were used as nontreated controls and the remaining 80 were divided into groups of 10 each and treated as follows:

Group 1: 100 mg. per kg. per day of PAS
Group 2: 200 mg. per kg. per day of PAS
Group 3: 400 mg. per kg. per day of PAS
Group 4: 800 mg. per kg. per day of PAS
Group 5: 10 mg. per kg. per day of thiocarbanidin
Group 6: 20 mg. per kg. per day of thiocarbanidin
Group 7: 40 mg. per kg. per day of thiocarbanidin
Group 8: 80 mg. per kg. per day of thiocarbanidin

The results of this experiment are shown in table 2.

It will be noted from table 2 that, on a weight-for-weight basis, considerably less thiocarbanidin is required than PAS to produce the same antituberculous effect in guinea pigs when the average index of tuberculosis is used for comparison.

Drug Toxicity

Thiocarbanidin showed no gross toxicity in rabbits if given for 194 days, or for guinea pigs if given for 150 days, when administered by mouth and in a dosage of 10 to 80 mg. per kg. per day.

TABLE 2

EFFECT OF THIOCARBANIDIN AND PAS ON TUBERCULOSIS IN GUINEA PIGS

Groups	Number of Guinea Pigs	Number of Survivors	Average Index of Gross Tuberculous Disease*
0 (Controls)	5	5	12.3
PAS 100 mg/kg/day	10	10	7.0
PAS 200 mg/kg/day	10	10	5.5
PAS 400 mg/kg/day	10	10	4.3
PAS 800 mg/kg/day	10	8	4.1
Thiocarbanidin 10 mg/kg/day	10	9	6.7
Thiocarbanidin 20 mg/kg/day	10	10	5.8
Thiocarbanidin 40 mg/kg/day	10	10	4.3
Thiocarbanidin 80 mg/kg/day	10	10	4.8

* Based on value of 0 to 4 for each of lungs, livers, spleens, and lymph nodes according to amount of gross tuberculous disease. Maximum was 16 for each animal.

Summary

Thiocarbanidin produced inhibition of growth *in vitro* of H37Rv, H37Rv resistant to isoniazid and PAS, and 4 freshly isolated strains of tubercle bacilli. The drug also inhibited the growth of 4 photochromogenic strains. An H37Rv thiosemicarbazone-resistant strain grew in the presence of thiocarbanidin.

When given orally to H37Rv-infected guinea pigs, thiocarbanidin was most effective in a dosage of 40 mg. per kg. per day. When used in combination with streptomycin or isoniazid, it was superior to either streptomycin or isoniazid alone. Isoniazid alone was superior to the combination of thiocarbanidin and streptomycin, but not quite so effective as the combination of thiocarbanidin and isoniazid.

Rabbits with miliary tuberculosis were benefited by thiocarbanidin, whereas PAS was ineffective.

On a weight-for-weight basis, considerably less thiocarbanidin is necessary than PAS to produce an equivalent antituberculous effect in guinea pigs.

Thiocarbanidin had little effect upon an infection produced by H37Rv thiocarbanidin-resistant tubercle bacilli.

Thiocarbanidin showed no gross toxicity for rabbits or guinea pigs.

Sumario

Actividad Antituberculosa de la Tiocarbanidina In Vitro y en el Animal de Experimentación

La tiocarbanidina produjo inhibición de la proliferación *in vitro* de H37Rv, H37Rv resistentes a la isoniacida y al PAS, y de 4 cepas recién aisladas de bacilos tuberculosos. La droga también inhibió la proliferación de 4 cepas fotocromógenas. Una cepa tiosemicarbazonorresistente de H37Rv proliferó en presencia de tiocarbanidina.

Al administrarse por vía oral a cobayos infectados con H37Rv, la tiocarbanidina mostró su mayor eficacia a dosis de 40 mg. por Kg. al día. Cuando se usó en combinación con la estreptomicina o la isoniacida, se mostró superior a una a otra por sí sola. La isoniacida sola resultó superior a la combinación de tiocarbanidina y estreptomicina, pero no tan eficaz como la combinación de tiocarbanidina e isoniacida.

Los conejos que padecían de granulia se beneficiaron con la tiocarbanidina, mientras que el PAS resultó ineficaz.

A base de peso igual, se necesita una cantidad considerablemente menor de tiocarbanidina que de PAS para producir un efecto antituberculoso equivalente en los cobayos.

La tiocarbanidina ejerció poco efecto sobre una infección producida por bacilos tuberculosos tiocarbanidinorresistentes de la cepa H37Rv.

La tiocarbanidina no reveló toxicidad macroscópica para los conejos o los cobayos.

Resume

Activité antituberculeuse de la thiocarbanidine in vitro et chez l'animal expérimental

La thiocarbanidine a produit *in vitro* l'inhibition de la croissance de H37Rv, H37Rv résistant à l'isoniazide et au PAS, et celle de 4 souches fraîchement isolées de bacilles tuberculeux. La drogue a également inhibé la croissance de 4 souches photochromogéniques. Une souche de H37Rv thiosemicarbazone-résistante s'est développée en présence de thiocarbanidine.

La thiocarbanidine administrée oralement au cobaye inoculé avec H37Rv s'est montrée des plus efficace à la dose de 40 mg/kg par jour. Utilisée en association avec la streptomycine ou l'isoniazide, elle s'est montrée supérieure aussi bien à la streptomycine qu'à l'isoniazide

administrées séparément. L'isoniazide seule était supérieure à l'association thiocarbanidine-streptomycine, mais elle n'était pas aussi efficace que l'association thiocarbanidine-isoniazide.

Les lapins atteints de tuberculose miliaire ont été améliorés par la thiocarbanidine alors que la PAS était inefficace.

Poids pour poids, il faut considérablement moins de thiocarbanidine que de PAS pour obtenir un effet antituberculeux équivalent chez le cobaye.

La thiocarbanidine n'exerçait que peu d'action sur une infection produite par un bacille tuberculeux H37Rv thiocarbanidine-résistant.

La thiocarbanidine n'a démontré aucune toxicité apparente chez le lapin ou le cobaye.

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A SMALL OUTBREAK OF HISTOPLASMOSIS[1]

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INTRODUCTION

On February 16, 1956, upon the request of a local physician to the State Health Department, an investigation was made of 3 cases of atypical pneumonia in Dallas County, Alabama. The 3 patients were a 36-year-old male, an employee of the State Conservation Department, and his two children, a 3-year-old girl and a 5-year-old boy.

CHARACTER OF ILLNESS

Onset of the illness for both children was on January 30. Vomiting, diarrhea, and hyperpyrexia were the predominant symptoms. The children were put to bed, and at the end of five days showed marked improvement and were allowed to be ambulatory. A physician was not called at this time, and the children received no therapy. However, because they continued to show anorexia, low-grade fever, sore throat, slight cough, and depression, medical aid was sought on February 16.

Roentgenograms revealed multiple densities throughout both lung fields, with marked enlargement of the peribronchial lymph nodes. Nodules throughout both lungs were not very densely calcified and were similar to those found in miliary tuberculosis except that they were much larger. Some of the nodules were barely visible, while others ranged up to 1.5 cm. in diameter. There was no history of recent contact with birds. Blood specimens were drawn to test for influenza *A* and *B*, psittacosis, Q fever, and histoplasmosis complement-fixation antibodies.

On February 3, the father developed symptoms similar to those of the children. He was admitted to the hospital on February 6 and was placed on penicillin-streptomycin therapy.

Roentgenograms, taken three days later, showed extensive but barely visible infiltration throughout both lung fields. This infiltration seemed to be along the lymphatics and was not definite enough to be considered pulmonary fibrosis or early miliary tuberculosis. A diagnosis of acute enterocolitis was made, and on February 10 the patient was discharged from the hospital, observation and treatment to be continued on an outpatient basis. He was readmitted to the hospital on February 13, where he remained until his death. Roentgenograms taken on February 14, five days after the first films, showed such extensive diffuse pulmonary infiltration that its diagnostic characteristics were obscured. Attempts to isolate virus from sputum specimens collected on February 16 and 20 were unsuccessful. Mycologic studies were not carried out at this time. The patient died on February 23, the twenty-first day of his illness.

Post-mortem examination: Post-mortem pathologic examination gave a positive diagnosis of diffuse pulmonary histoplasmosis with mild generalized congestion and splenic infarct. Gross examination of the lungs showed that they were completely consolidated and gran-

[1] From the Laboratories, Alabama State Health Department, Montgomery, Alabama; United States Public Health Service, Communicable Disease Center, Mycology Unit, Chamblee, Georgia, and Veterinary Section, Montgomery, Alabama.

TABLE 1

RESULTS OF COMPLEMENT-FIXATION TESTS FOR HISTOPLASMOSIS ON THE FATHER AND TWO CHILDREN

Patient	Date	Yeast Phase	Histoplasmin
K. D.	2-13-56	1:256	—
	2-20-56	1:512	1:16
J. D. (daughter)	2-13-56	1:64	—
	5-16-56	1:32	—
K. D., Jr. (son)	2-13-56	1:32	1:8
	5-16-56	1:64	1:64

ular. The normal spongy pulmonary architecture was completely replaced by a relatively homogenous reddish-gray parenchyma, which showed small white nodules scattered diffusely throughout.

Microscopic examination of sections of the lobes of the lungs showed the alveolar spaces filled with fibrin, and inflammatory cells. Among the latter were numerous large phagocytes containing yeastlike cells typical of *Histoplasma capsulatum*. This histologic finding was later confirmed by isolation of the fungus from tissues obtained at autopsy.

Complement-fixation tests were made on specimens from the father and from both children. For the father, test results were negative for viruses but positive for histoplasmosis. A titer of 1:256 was obtained with the yeast-phase antigen, while the histoplasmin antigen gave negative results. The blood specimens from both the daughter and son also were positive for histoplasmosis. The results of the complement-fixation tests are summarized in table 1.

After the father's death, the family moved to Oklahoma. There, on February 29, 1956, in a follow-up examination of the children, chest roentgenograms showed the infiltration still present, but with remarkable clearing. The mother reported that the children were completely well. Roentgenograms and serologic tests on the mother for histoplasmosis were negative.

EPIDEMIOLOGIC STUDIES

Epidemiologic investigation indicated that manure, collected by the father from an undetermined site, probably was the source of infection. He had collected it on a field trip and had transported it in the car. On January 15, when he returned home, he and the children unloaded the manure and spread it on their flower beds. The mother recalled his saying that he had obtained the fertilizer near an old abandoned chicken house. However, gross examination of the material did not definitely determine what type of manure it was.

Two soil samples were collected from the flower beds and *H. capsulatum* was recovered from them both by the following procedure:

From each of the samples, approximately 10 ml. of a thoroughly mixed specimen was suspended in 30 ml. of sterile physiologic saline containing 5,000 units of penicillin and 1,000 units of streptomycin per milliliter. Five milliliters of the supernatant were removed after a settling period of approximately one hour. Each of 4 mice was then injected intraperitoneally with 1 ml. of the supernatant (a total of 8 mice for the two soil samples). Eight weeks following inoculation the mice were sacrificed, and small pieces of liver and spleen were cultured on duplicate tubes of a neutral peptone-dextrose agar containing 0.05 mg. of

chloramphenicol per milliliter (neopeptone, 1 gm.; dextrose, 1 gm.; chloramphenicol, 5 mg.; agar agar, 2 gm.; distilled water, 100 ml.; adjusted to pH 7). The tubes were incubated at 25° C. and examined periodically for pathogenic fungi. *H. capsulatum* was recovered from each of the 8 mice injected with the soil suspensions.

Discussion

About forty outbreaks of histoplasmosis have been reported in the United States since 1938 (1, 2). Undoubtedly, many infections are misdiagnosed, and many that present only mild symptoms are missed entirely. Such could have been the case in this instance had the father's illness not been fatal. In the areas endemic for histoplasmosis, it appears vital that a provisional diagnosis of histoplasmosis be considered in all acute respiratory infections.

Many investigators (3–6) have verified the association of *H. capsulatum* with soil from avian habitats, an observation first made by Zeidberg and associates (7). Public health workers and physicians should be aware of the distinct hazard that chicken houses present directly to farmers and their families and indirectly to others. In many of the reported outbreaks, persons infected with *H. capsulatum* had participated in cleaning out chicken houses, towers, or other enclosed areas contaminated with bird droppings. In the report of Kier and co-workers (8), an acute episode of histoplasmosis in an individual was traced to the handling of chicken manure purchased by a city dweller for use as a fertilizer for flower beds.

Histoplasmin skin test surveys (9) show that Alabama has a significant number of reactors among its population. The state can be divided into four zones, according to the rates of histoplasmin reactivity (figure 1). Reaction percentages vary from 2 to 10 per cent up to 60 to 80 per cent. Dallas County, where the cases under discussion occurred, is in the 30 to 60 per cent zone.

During 1956, two other deaths attributed to *H. capsulatum* were recorded in the state: one a Negro male from Dallas County; the other, a 36-year-old white woman in Jefferson County. The figures for 1957 are not yet available.

Since histoplasmosis is endemic in Alabama and the prevalence rate is high, physicians there should consider this disease in the differential diagnosis of pulmonary infections, along with psittacosis and other diseases. Although the number of cases of psittacosis which occur in Alabama is exceedingly small, that disease is regularly considered in cases of atypical pneumonia. In addition, surveys of the state's parakeet-raisers by means of complement-fixation tests do not reveal any marked occurrence of psittacosis, even among this high-risk group.

It is important to emphasize that chicken habitats are favored sites for the growth of *H. capsulatum* and that persons engaged in raising chickens should take precautions to avoid infection. The measures advocated by Lehan and Furcolow (1), which include wetting down chicken houses before cleaning them, are simple to follow and should serve to reduce or prevent infections. The public in general should be made aware of the potential infectivity of chicken manure. Urban residents, who ordinarily have had no previous exposure to *H. capsulatum*

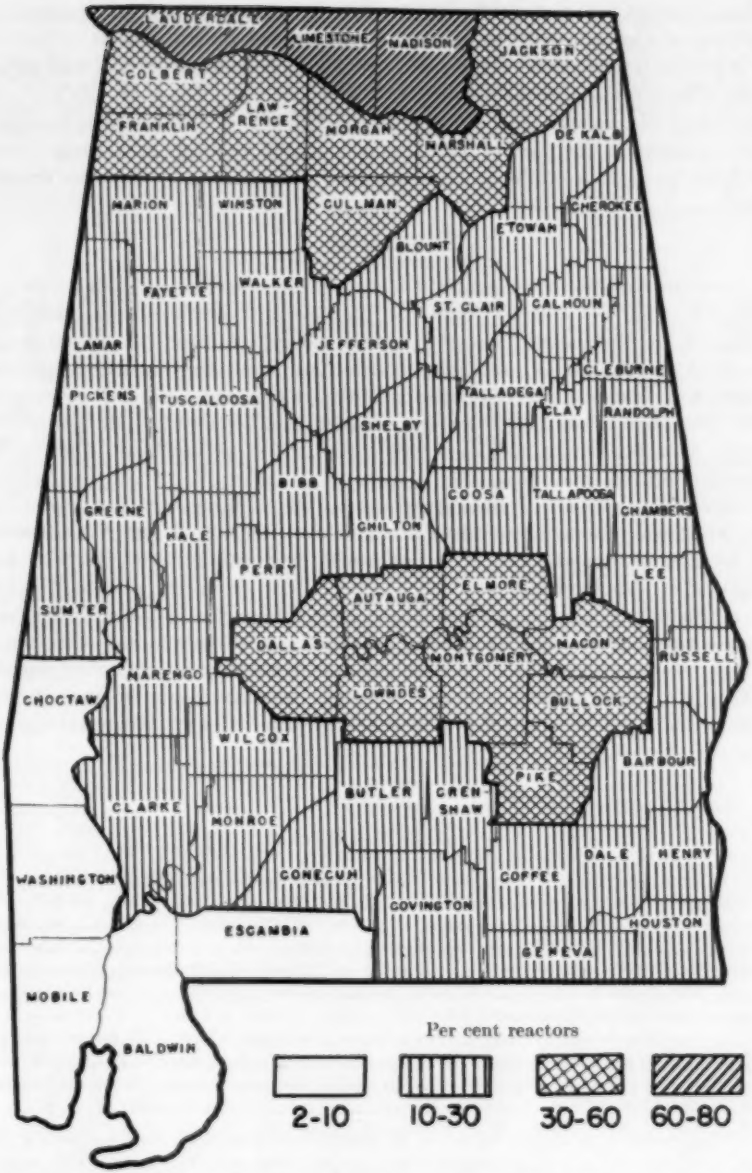

FIG. 1. Distribution of Alabama counties according to percentage of young histoplasmin reactors (adapted from Manos *et al.* (9)).

—hence, have no resistance—may develop severe or fatal illness through inhalation of spores that develop in soils enriched with bird manure.

With the introduction of the antimicrobial, amphotericin B,[2] the first apparently effective therapeutic agent for the treatment of histoplasmosis and systemic mycotic diseases has become available (10–12). It is imperative, therefore, that an accurate diagnosis of histoplasmosis should be established early so that prompt application of therapy can obviate prolonged hospitalization or even death.

Summary

An epidemiologic investigation of 3 cases of histoplasmosis, which involved a father and his two children, indicated that manure (probably from chickens), collected by the parent, was the possible source of infection. Symptoms of atypical pneumonia, i.e., marked anorexia, low fever, sore throat, cough, and depression, developed in all 3 patients, fifteen to nineteen days after they spread the manure on flower beds. Roentgenographic studies revealed pulmonary densities. A viral infection was considered to be the cause of illness. The father's infection proved fatal.

Mycologic studies were not carried out on the children or on the parent during his illness. Complement-fixation studies for influenza *A* and *B*, psittacosis, Q fever, and histoplasmosis were performed. Only the histoplasmin tests were positive. *Histoplasma capsulatum* was isolated from the parent's tissues obtained at autopsy and from two soil samples collected from the fertilized flower beds.

It is urged that a provisional diagnosis of histoplasmosis be considered in all acute respiratory infections. Since an apparently effective antimicrobial, amphotericin B, is now available, prompt diagnosis becomes urgent so that therapy can be initiated in time. The public health hazards of chicken habitats and manure are emphasized.

Sumario

Brote de Histoplasmosis

Una investigación epidemiológica de 3 casos de histoplasmosis en un sujeto y sus dos hijos indicó que el estiércol (probablemente de gallinas) recogido por el padre, era la posible causa de la infección. En los 3 enfermos, de quince a diecinueve días después de esparcir el estiércol en los arriates del jardín, aparecieron síntomas de neumonía atípica, a saber, anorexia notable, febrícula, angina, tos y abatimiento. Los estudios roentgenográficos revelaron zonas pulmonares de condensación. Se consideró que una infección viral era la causa de la enfermedad. La infección resultó letal en el padre.

Durante la enfermedad paternal, no se hicieron estudios micológicos ni en el padre ni en los hijos. Se ejecutaron estudios de fijación del complemento para influenza A y B, psitacosis, fiebre Q e histoplasmosis. Las pruebas con histoplasmina fueron las únicas positivas.

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[2] Manufactured as Fungizone by E. R. Squibb and Company, New Brunswick, New Jersey. (Trade names are used for identification purposes only. Mention of them does not constitute endorsement by the Public Health Service.)

Se aisló el *Histoplasma capsulatum* de los tejidos obtenidos en la autopsia del padre y de dos muestras del suelo recogido de los arriates abonados.

Encarécese que se considere un diagnóstico provisorio de histoplasmosis en todas las infecciones agudas del aparato respiratorio. Como ya se cuenta con un antimicrobiano aparentemente eficaz, la anfotericina B, la prontitud en el diagnóstico es urgente a fin de iniciar la terapéutica a tiempo. Recálcanse los riesgos sanitarios que entrañan las habitaciones y los excrementos de las gallinas.

Resume

Une épidémie d'histoplasmose

Une enquête épidémiologique sur 3 cas d'histoplasmose concernant un père et ses deux enfants a indiqué que du fumier (provenant probablement de poulets), accumulé par le père, pouvait être la source de l'infection. Des symptômes de pneumonie atypique c'est-à-dire anorexie prononcée, fièvre légère, angine, toux et asthénie se sont produits chez les 3 patients quinze à dix-neuf jours après étalement du fumier sur un parterre de fleurs. Les études radiologiques ont révélé des opacités pulmonaires. La cause de la maladie a été attribuée à une infection virale. Chez le père l'infection a été fatale.

Il n'a pas été fait d'études mycologiques chez les enfents ou le père durant la maladie. Des tests de fixation du complément pour influenzae *A* et *B*, la psittacose, la fièvre Q et l'histoplasmose ont été effectués. Seuls les tests à l'histoplasmine ont été positifs. L'*Histoplasma capsulatum* a été isolé des tissus du père obtenus à l'autopsie et de deux échantillons de terre prélevée sur les terrains fertilisés.

On recommande vivement de considérer temporairement le diagnostic d'histoplasmose dans les infections respiratoires aiguës. Etant donné qu'un antibactérien paraissant efficace, l'amphotéricine B, est actuellement disponible, un diagnostic précoce est urgent pour permettre d'instituer le traitement à temps. Le danger représenté par les poulaillers et les déjections de poulets en hygiène publique est souligné.

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THE ARCANA OF TUBERCULOSIS

With a Brief Epidemiologic History of the Disease in the U.S.A. Part IV.

E. R. N. GRIGG

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IV. Practical Remarks Regarding the Epidemiology of Tuberculosis*

Tuberculosis had existed among American Indians since time immemorial, but it occurred infrequently as long as they kept on touring their hunting grounds, and it turned to spiking only when they were corralled in reservations or otherwise changed their ancestral habits. The early settlers brought tuberculosis with them, tucked away in their prairie schooners, but the disease was infrequently encountered in the Midwest until railroads began to link the seaboards, and the Industrial Revolution steam-rolled over the prairie. The Southern Negroes, while living the secluded life of slavery, suffered infrequently from tuberculosis but, when emancipation sent them to the cities, their specific death rates began to climb hastily. (Parenthetically, it might be noted that the South African Bantu are another excellent demonstration that a virgin population, even when infected with tuberculosis, will not see its death rate soar overnight unless an additional factor supervenes to cause a "change in reactability.")

For centuries, the climate had been incriminated as the major cause of the variations in the incidence of tuberculosis in given locations. However, in the face of significant racial differences in tuberculosis mortality within a given location, the climatic factors should have been removed from the list of major determinants in phthisiogenesis. This viewpoint was adopted one century ago by Colegrove (129), which did not prevent the subsequent, fervid promotion of the high and/or dry air of certain health resorts (130, 131), perhaps not always without pecuniary motivation on the part of the respective writers.

Even so, the higher incidence of tuberculosis at given times and in certain places had to be explained.

Some of the assertions were obviously biased; for instance, the belief that vaccination with cow-pox lymph from cachectic children had been responsible for an alleged increase of consumption in New York in the 1830s and 1840s (132).

Many authors, including one of the greatest American students of clinical pulmonary disease, Austin Flint (1812–1886), mention that, in the United States, there was a predominance of tuberculosis in females (133), which lasted almost to the end of the nineteenth century (figure 28).[1]

This apparent predilection to tuberculosis in the distaff elicited many peculiar interpretations. In the late 1700s, Dr. Gregories believed it was caused by prolonged reading

* Parts I, II, and III have been published in two preceding issues of the Review.

[1] The Providence, Rhode Island, data were contributed by Dr. Joseph Smith, Superintendent of Health of the City of Providence.

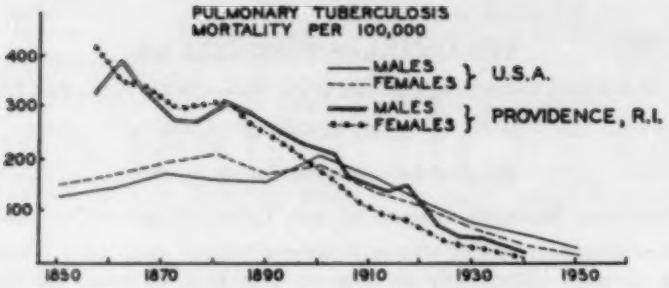

FIG. 28. Until 1900, in the United States, tuberculosis mortality was higher in the female, while since that time it has been constantly higher in the male. In the city of Providence, Rhode Island, this change of phase occurred about two decades earlier, indicating that the degree of urbanization may possibly exert some influence in this matter. Interesting to note is the temporary reversal to a higher tuberculosis mortality in the males of Providence during the Civil War. *Source:* National Office of Vital Statistics and City of Providence Health Department (*see* also footnote 1).

of romantic prose: "And many young ladies, who regardless of exercise, customary meals or necessary repose, are perpetually employed in reading love-inspiring novels, not only impair their constitutions, but pervert their imaginations, and corrupt their morals to such a degree, that they are ever after rendered unfit for the offices of domestic life, and unqualified to promote domestic felicity." (62). Another author claimed that the sexual excesses of female Eskimos (with Russian colonists in Alaska) were the reason for their higher susceptibility to tuberculosis than that of their male (Eskimo) counterparts (134). A short-lived elucubration by King (135) assumed that lowered respiration caused atrophy of the body by adaptation of the organism to lowered requirements. Sometimes this atrophy would transgress its boundaries and turn into phthisis. (In the caustic words of Busey, this theory was not based on either experience, post-mortem examination, or experiment, but was a mere fabrication.) In the late 1800s, tight lacing was thought to cause the higher tuberculosis mortality in the female: "This, it is submitted, is a frightful record, and shows what a dreadful penalty the race must pay when ignoring and directly violating the physiological laws of life. At this age, pectoral breathing is forced upon the female..." (136). For many decades afterwards, boned, hooked, and/or laced corsets perpetuated the contention of exuberant busts, and lent support to bulging waistlines; but after only a few years, the prevalence of tuberculosis mortality in the female, which has been a phase aspect, reverted to a male predominance.

As stated previously, the increased tuberculosis mortality in urban centers had been acknowledged in Germany by the middle of the eighteenth century.

The high incidence of consumption in the big cities had been presented with reference to New York by Delafield (107) in 1816; with reference to Washington by Antisell (137) in 1868 (including sad remarks about the country boys who accept government positions "and hope that $1200 or $1400 will make them glitter"); with reference to Chicago by Johnson (138) in 1877 (who discussed the impact of the density and modes of living of the immigrants in the early 1850s); and with reference to Philadelphia by Flick (139) in 1892. Flick (140) also claimed that "the house is the granary of the tubercle bacillus outside of its host. Were it not for the house, the tubercle bacillus would soon perish from

the face of the earth." This concept of the tuberculosis-harboring room or house is very old, and one of its earliest mentions can be found in the observation of Luzuriaga (a physician from Bilbao, Spain) who reported in 1787 the death from consumption of several nuns who had successively occupied the same cell (141).

In fact, a relationship seems to exist between the density of the population and the height of the tuberculosis death rate (142), which, of course, obtains only during and immediately after the epidemic stages of the wave. More recently, epidemic tuberculosis was considered coterminous with the development of the modern industrial system; the hygienic, social, and economic concomitants of industrialism being incriminated as the responsible factors (143). As summed up, tuberculosis would be the result of incomplete civilization (144). These are all phase aspects.

The Indians, the homesteaders, and the Negroes had suffered from tuberculosis for a long time, but, initially, the incidence of the disease had been at a low ebb. The sudden change in pace seemed to have an ecologic motivation. The environmental change cannot be assumed to act upon the microorganism: increased virulence of urban strains of *M. tuberculosis*, as opposed to rural strains, is untenable as an hypothesis because of the ubiquitousness of the agent. The bionomical influence must have been exerted upon the terrain, i.e., it must have modified (magnified) the reactability potential of the host's tissues.

In 1855, Thomas Reyburn (1819–1855), in discussing the spread of cholera, postulated that the newly arrived immigrants must first come in contact with an imaginary *crowd poison* (145) before they could contract the disease. In tuberculosis, such a "crowd poison" could be termed any combination of the factors included in the term *urbanization* (*see* above). As previously stated, the mode of action could be related to altered secretion of steroid hormones. From a psychiatric viewpoint, the result resembles very often what has been called a "situational crisis" (146). All of those who have had clinical experience with tuberculosis in a metropolitan area, or among prisoners, know that this is a highly significant factor in phthisiogenesis.

There appears to be a relationship between the level of innate immunity and the degree to which this might be altered by intervening events. Toward the end of the tuberculosis wave, there are fewer individuals who can be influenced by the "crowd poison." At that point, even acute episodes of urbanization (war!) cause but an insignificant number of added cases.

Withering Tuberculosis

It is not unusual to underestimate the perspicacity of, and the knowledge attained by, previous generations. Surprising as it may seem, both physicians and statisticians realized very soon after 1800 that tuberculosis had started to decline in some areas of the United States. Perhaps the earliest such observation was made in conjunction with Morgan's life insurance figures based on the records of the Equitable Assurance Company[2] (147).

[2] Nevertheless, even in 1875, Davis stated that "Phthisis pulmonalis is, of all diseases, the one which life insurance companies most fear." (148). In recent years, this "actuarial anxiety" resulted in considerable interest devoted to the numerical aspects of tuberculosis by the Metropolitan Life Insurance Company, and especially by its former (now retired) vice-president and expert statistician, Louis I. Dublin.

The decrease was difficult to assess as long as the data comprised only relative mortality (mortality from tuberculosis compared with mortality from all causes), and not the absolute mortality (mortality from tuberculosis with reference to the number of living population) (149). This may explain why, for a long time to come, tuberculosis continued to be regarded as a stable calamity, depicted in the flowery style of the 1870s by Meriwether Lewis of Lenoir, Tennessee: "The great Sphinx question of modern times is Pulmonary Consumption. For centuries past it has continued to devour its helpless victims, while as yet no Theban hero has appeared whose genius or profound research could solve the dreadful enigma." (150). The euphonic lament notwithstanding, tuberculosis decreased steadily, and when adequate statistics became available, this fact was properly demonstrated (151). Nevertheless, the absolute figures were still high enough to warrant the overtly lachrymogenic approach employed in obtaining a substantial slice from public and private monies to be used in the "attack" against the disease.

In 1926 the figures reached a low which drew a noteworthy (but premature) editorial comment: "Tuberculosis in fifth place of killing diseases embodies really a new concept. It is not easy to get as excited as of old over a disease well down on the list. We must surely find it more difficult to enlist sympathy and active aid in the combat against what is approaching the foot of the scale of major ailments." (152).

More recently, it was stated that tuberculosis in this country is falling at a rate faster than ever in known history. This impression was gained by comparing the higher than expected tuberculosis death rates encountered during World War II with the (below average) post-war figures. A similar statistical pitfall had caused some confusion after the previous war. In any event, today in the United States the tuberculous pandemy is withering away noticeably.

What Caused the Decline of Tuberculosis?

As the tuberculosis figures were decreasing, some explanation had to be offered. In 1904, Hoffman (an actuary of the Prudential Insurance Company) attributed the decrease to vast and far-reaching improvements in housing and infant feeding, to the abolishment of child labor, and to the over-all economic betterment (114). Drolet (a statistician from New York) in 1924 admitted the influence of heredity upon the decrease of tuberculosis mortality, but stated that the improvement of social conditions yields far greater gains (153). In 1938, he found no evidence that medical and surgical treatment had any influence on the fatality rate or, for that matter, on the statistical decrease of the death rate (154). In 1952, Drolet studied the "community case fatality rates" of various countries and concluded that these were considerably improved by comparison with the situation of 1940, presumably as a result of antimicrobiol therapy (155). Finally, in 1955, he dwelt at length on the significance of the decrease which had occurred in the span of seven years, based on 1947–1953 statistics, believing this to be a demonstration of the effectiveness of antituberculous therapy (156). While the latter contention may or may not be essentially correct as far as the effectiveness of chemotherapy

is concerned, it is certainly unwise to base any statement of this magnitude on the examination of seven yearly rates: a wooded area is easily surveyed from an airplane, while on the ground one cannot see the forest because of the trees. It is all a matter of perspective and, in the case of tuberculosis, it takes a secular curve to draw any conclusions at all.

In the opinion of L'Eltore, the increase in mortality due to heart diseases, coincident with the decrease of the tuberculosis rate, must be considered as a symptom of progress in the status of public health (157). A very diplomatic approach is used by Esmond Long, who states that nobody could deny that present-day measures of public health and phthisiotherapy *contribute* to the most recent sharp decline of tuberculosis (158). Similar views are held by Woodruff, who credits the improvement in working conditions for the decrease of tuberculosis mortality in the twenty-five to thirty-four-year age group,[2] and believes that the advent of chemotherapy has influenced the over-all tuberculosis rates (159). A recent survey made jointly by the Public Health Service and the National Tuberculosis Association reported (on October 30, 1957) that there has been a decline of almost thirty per cent in cases of active tuberculosis in the United States in the last five years, and expressed the belief that this decline is attributable to more effective chemotherapy and better disease control methods.

The causal relationship of these factors holds certain similarities with the use of a flashbulb to remove the contrasty shadows from the face of a subject photographed in bright sunshine: The flashbulb (which would represent the chemotherapy and the public health measures) *contributes* a certain amount of light, properly distributed and quite effective for its own limited purpose, but the overall picture is determined by the obviously brighter sunshine (which would thus represent the natural selection of those susceptible to tuberculosis).

Shortly after general acceptance of the doctrine of contagion, an optimistic attitude began to prevail. This may be seen from the statement of Flick (139), who believed that "tuberculosis is of all diseases the most easily preventable. All that is necessary is to confine this (tuberculous) pus, and the most intimate relations between sick and well can be safely maintained." A few years later, the New York Board of Health passed a resolution requiring a report of all cases of pulmonary tuberculosis; then it was suggested that a "White City" be created (in Colorado, New Mexico, or California) for all of the tuberculous in the United States; in fact, Alfred Walton (of New York) thought "it would be a simple matter to stamp out pulmonary tuberculosis by the removal of all such cases to a dry atmosphere in a high altitude." (160). The magnitude of such an enter-

[2] Woodruff (159) states that the peak in cohort mortality has shifted over the years from the twenty-five to thirty-four to the fifteen to twenty-four age group. Figures calculated in this manner, without taking into consideration the racial composition are hazardous to interpret. There is certainly a difference in the tuberculosis death rates of Negroes, Indians, Mexicans, et cetera, when compared to the so-called Caucasians, and there is also a noticeable difference in the distribution of the age groups among these populations. These two sets of differences must not necessarily annulate themselves in the calculation of specific death-rates by age groups; on the contrary, they may confuse the issue, as they probably have.

prise would make it a practical impossibility even at today's much lower rates of incidence.

In the meantime, a wave of tuberculophobia encompassed the globe, from Florence (161) to Lemberg (162), from Barcelona (163) to Calcutta (164), and from Africa (165) to Hawaii (166). In this country, it culminated in the unfortunate (and later repealed) Goodsell-Bedell law. In 1909, the State Board of Medical Examiners of Oklahoma decided that"tuberculous but otherwise well-qualified practitioners were to be excluded from practising in that state, and physicians were forced to sign a sworn statement that they had not in the last three years lived in the house with or nursed any one suffering from said disease"[4] (167).

An irate eugenicist recommended that "men and women possessing the tubercular predisposition refrain from giving birth to children" (168). After studying tuberculosis in the Orient, a phthisiologist stated that "good hygiene, however important and highly desirable, is of distinctly minor importance in comparison with an optimal tuberculization" (18). Certain plant diseases can be eradicated by infecting the plants on purpose and by subsequently inbreeding the survivors, i.e., the "insusceptibles"; a bacteriologist, who used this comparison, did not advocate this method in human tuberculosis, but requested that infection of the tuberculo-susceptibles be artificially prevented (169). So far, unfortunately, there is no known method to identify the tuberculo-susceptibles except in retrospect.

It is generally accepted that tuberculosis is spread almost entirely by patients with pulmonary disease who are coughing up sputum containing the microorganisms. "Until these people have been found and cared for, the real job has not been done" is the quintessence of the so-called modern program (170). This sounds logical, and is even feasible in a circumscribed rural territory (171). It is, however, impossible on a nation-wide scale, even with a considerably larger financial outlay than is presently available. To amplify the argument, the statement is made that "tuberculosis is a sound investment for public health money," but in that particular article (172) the figures are dated prior to 1945, when the death rates were inflated by World War II. In the face of a dwindling incidence, any generalized detection method becomes economically unsound. Even so, some writers intimate that, by following these procedures, tuberculosis will be "eliminated" in the next fifty years or so (173).

The Significance of "Social" Factors in Tuberculosis

Any discussion under this heading requires first of all a clarification of the meanings involved.

The concept of *social* (not socialized) *medicine* cannot be retraced to the Thermidorian revolutionary Gracchus Babeuf (1760–1797), but it began to take shape around the

[4] Today the respective requirement of the Oklahoma Board is formulated ". . . applicant . . . must present satisfactory evidence . . . that he is not suffering with active tuberculosis." In response to a written inquiry in 1955, the secretary of the Oklahoma Board replied that, as far as the records in their office disclose, the portion of the statement "physicians were forced to sign a sworn statement" is without foundation.

middle of the nineteenth century as a direct outgrowth of the progressive spread of socialistic ideas, which at that time were undoubtedly justified by the prevailing conditions of labor at the start of the Industrial Revolution. This social interest in health could not make use of hereditary phthisis as an argument, and had to await the disclosure of its contagious nature. By then, the medical leaders became so imbued with the bacterial etiology that all other pathogenic possibilities were hastily discarded. Ironically enough, the anti-contagionistic "medical reactionaries" had to push the *social* into the tuberculosis picture, in the hope that this would counteract the importance of the bacillus by implying that the environment could modify the constitutional background. The political value of such implications and the success of its exploitation are history.

Frequent repetition of any good-looking catchword will qualify it for admission into a decent vocabulary, which is tantamount to being accepted at face value. As a result of such a repetition, the social components in phthisiogenesis cover a wide range, and include all those political and economic factors which may influence the health (recently also the happiness, because there are psychosomatic possibilities even in tuberculosis) of the population-at-large, and of the low-income groups in particular. While this is a big order in itself, its sidelines (called Social Science) have assumed such a widespread acceptance that it has become hazardous to question the validity of any of these assumptions. But then, this should hardly come as a surprise. Mixing medicine and politics is like borrowing money from relatives: repayment of the debt, even with excessive interest, cannot remove all contingent obligations.

The alleged social implications of tuberculosis have often been used as a means of exerting political pressure, which was perhaps best expressed by the late hygienist Haven Emerson (1874–1957): "But after all our specific and accessory factors have been employed we shall still in all probability fall short of the full possibilities of applied medical and sociological effort if we do not put our utmost weight on the side of economic justice to the wage earner, and a more generous sharing of the profits of industry with the producer." (174) It is difficult to draw the line between sincere personal belief and political servitude (even congressional investigations are said to have failed in the attempt to separate the two issues in specific instances). It is easier to remove the gist of the argument with a single stroke: The decrease of tuberculosis does not require any particular political constellation, because the death rates are falling in all countries around the globe, whether forward or backward, agricultural or industrial, democratic or dictatorial.

Moreover, there remains the possibility that the various concomitants, assembled under the term of living standard, may still have the importance of adjuvant factors. This is the central theme of Dubos and Dubos (144), who contend that social environmental factors, directly or over genetic channels, may have had a significant role in shaping the tuberculosis phenomenon over the past 150 years.

This is correct to a certain extent. In fact, these factors are included in the preceding text under the generic term of *urbanization*, which includes their most damaging components. When acting at the beginning of the tuberculosis wave, poor living standards will speed up selection, i.e., accelerate the ulterior drop. As the potential reactability falls below significant levels, the "social components" become less and less important. Actually, even at the height of their glory,

it appears that most of their harmfulness is contained in the "change of reactability" (here is where the psychosomatic enters the picture) caused by the unfamiliar environment, which ought never to be underestimated.

Effectiveness of Antituberculous Procedures

In the large Eastern seaports, tuberculosis mortality began to decline one hundred years before any organized attempt was made to "fight" the disease. This, in itself, would not preclude the theoretic possibility that "antituberculous measures" might help to reduce the incidence of the disease. Even today, though, the isolation of "open cases" is totally inadequate. A recent press release (175) reported that there were about 10,000 known active cases of tuberculosis in Chicago (2,500 of them in hospitals), and *an estimated 5,000 unknown cases.* If these figures are multiplied by the peculiarities of human intercourse in a modern metropolitan area (and most of the "open cases" inhabit the densely populated tenement houses with recent migrants from the South and immigrants from Mexico and Europe), there remains little doubt about the ubiquitousness of *M. tuberculosis*, i.e., about its actual availability for the infection of practically everybody who lives in a metropolitan area. The nation-wide survey suggests that in 1956 some two million persons in the United States were ill or had been ill with tuberculosis. Of this number, 250,000 had active tuberculosis, requiring constant supervision and periodic re-check, and 1,200,000 once had active disease but were not now in need of close supervision. *Of the 250,000 patients with active tuberculosis, 40 per cent were not receiving any type of care, or were unknown to medical and health authorities.* Nevertheless, tuberculosis death rates are dwindling, both nation-wide and in Chicago.

The tuberculosis death rates in the United States are quite low, which is evident especially in the younger generations[5] (figure 29). Some have claimed that there has been a recent increase in tuberculosis morbidity in the cities and that the drop in death rates was the result of a reduction in "case fatality rates" following intensive use of antimicrobials. It is true that a transient increase in the incidence of tuberculosis occurred in the United States during World War II and its "hump." Since every real deflection constitutes a miniature wave, and exhibits the prescribed delays in the successive (not synchronous!) miniature peaks of mortality, morbidity, et cetera, it must be expected that the post-war decline in the number of new cases will be likewise delayed for several years after the peak of the death rate. The transient increase in tuberculosis morbidity in post-war United States has been detected in connection with some of the mass surveys, but it was sometimes obscured by migratory movements of the population and by statistical considerations of the observers.

Even if the entire bacilliferous population of the United States (estimated at 250,000 persons) was to be isolated at a moment's notice, this could not stop the

[5] These and other figures have been courteously offered by Mr. I. M. Moriyama from the National Office of Vital Statistics in Washington, D. C. The graphs for the entire paper have been traced by Mr. Edward J. Zagorski, Art Instructor in the University of Illinois in Champaign.

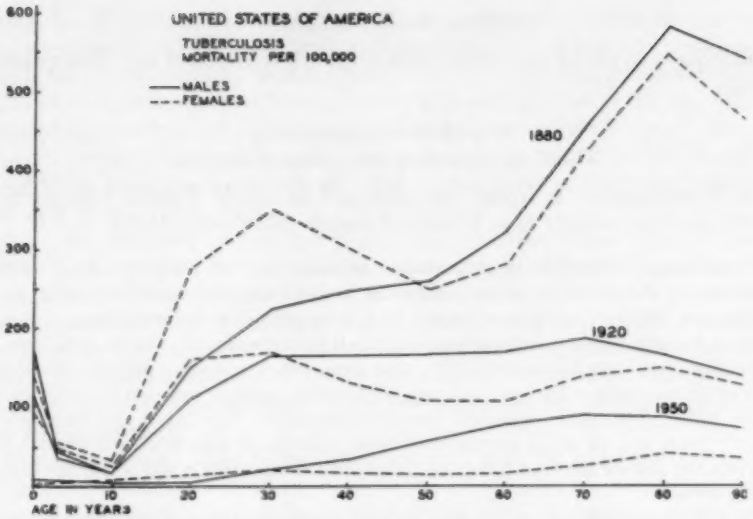

FIG. 29. The years 1880, 1920, and 1950 have been selected to approximate as closely as possible the ideal situations demonstrated in figure 4. Today, the population of the United States is approaching the levelling-off stage of the tuberculosis wave. *Source:* National Office of Vital Statistics (*see* footnote 5).

occurrence of new cases from the reservoir of inactive or undetectable lesions. The system of surveillance needed to implement a truly complete program must be so elaborate as to exceed by far the hazards incurred if there were no program at all. Evidently, if isolation of all contagious cases is not feasible today on a nation-wide scale, it is highly recommended for secluded environments, such as mental institutions, schools, prisons, et cetera, where public health measures could conceivably achieve the 100 per cent effectiveness so dear to the theorist (in practice, though, they never do).

Those who wish to oppose the opinions expressed in this paper are invited to disregard the logic behind the "time-honored and time-tested principles of tuberculosis control" and to consider only the factual inability of all of these efforts (which have never succeeded) to alter the inexorable pathway of the specific death rate during the past two centuries.

As the wave advances, the number of bacilliferous individuals will decrease. Up to a point, continuous urbanization will compensate for the fewer sources of infection by an increase in the number of contacts, but then the time shall come when the "open cases" will become sufficiently rare to make actual isolation possible. By then, the general immunity of the population should be so high that the matter may have little or no consequences. Certainly, a new wave of tuberculosis could always start (with a newborn strain of different antigenic composition), but this is unlikely in a biologically aging population (3).

What Should Be Done?

This question will be approached with genuine humility, and only after quoting Horace:

Si quid novisti rectius istis,
Candidus imperti; si non, his utere mecum.[6]

BCG vaccination is highly recommended in World Health Organization circles, and has recently been advocated even in this country (176).

Considering the number of authoritative stentors who are ready to certify to the reliability of the numerous controlled studies it would appear unwise to question their conclusions without having any "series" to make a point. On the other hand, it would amount to using circumstantial evidence if one should mention that most of the honest convictions regarding the value of BCG were formed at a time when peroral administration of the vaccine was the approved way, a procedure which is considered totally inadequate today. This same procedure, however, seemed to have given excellent results twenty years ago, or would anyone dare to say that those reports were fictitious? For the records, and for the time being, the value of BCG vaccination will be neither denied nor admitted.

If BCG were as effective as has been claimed, it still could not influence the epidemiologic outcome in this country, unless it were administered on a nation-wide basis. Today there is a bear's market for tuberculosis, sanatoriums are being closed or converted and it is hardly conceivable that the needed number of "bulls" could be rounded up to purchase enough of the falling stock for the universal use of BCG in this country.

Since the use of BCG produces few untoward reactions, and even fewer accidents, one may, if not in entire agreement with, at least condone the suggestions of the recent committee to employ BCG in exposed groups in the United States (176). This policy can always be changed should unexpected occurrences supervene.

But the big problem remains whether to oppose or encourage the natural selection of those who are susceptible to tuberculosis. Is it (theoretically) preferable to favor the contemporary or the future generations? What is good and what is bad?[7] Fortunately, it is still beyond our capabilities to really interrupt the selective process, and we do not have to make this decision; but, within the realm of available potentialities, could anybody refuse to isolate "open cases," with the intent to further selection? This must be answered in the negative: Whatever ethics might become acceptable one or two thousand years from now, today all our written and unwritten principles are definitely against such sacrifice.

Individual suffering must be minimized with all the means at our disposal. To offer this commodity, it must not be necessary to evoke threatening political and social consequences or to promise substantial returns on investments in

[6] These are the final sentences of the letter of the aging Horace (*Epistles* 1, 6, 67) to Numicius, in which he preaches "wise indifference," and concludes by saying: "If you know something better than these precepts, pass it on to me; if not, join me in following these."

[7] Hamlet (2, 2, 259) says "There is nothing good or bad, but thinking makes it so!"

public health monies. The detection and the treatment of active and/or contagious disease must continue unabated. And since it is not in our province to decide who is supposed to be subjected to the test of contamination and when, isolation of bacilliferous individuals must be provided. In view of the low yield of routine chest surveys of the entire population,[8] these may be applied only to exposed groups, while routine chest roentgenograms should be continued in hospitals (general, mental, et cetera). Skin testing could probably be employed on a larger scale than before.

With the practical disappearance of medical collapse procedures, the treatment of tuberculosis is restricted to chemotherapy, followed sometimes by surgical removal of stabilized or uncontrollable residuals. With the continuous increase in the number of survivors and in their survival time, which is inherent to this stage of the tuberculosis wave, more and more emphasis will have to be placed on rehabilitation and follow-up procedures. It might be wise to assign this task to general practitioners, while comparatively few centers may direct the entire program.

This over-all plan could be modified, but what must be preserved is the true perspective of cause-effect relationships in the tuberculosis phenomenon, if only to avoid the charge of gullibility, which might be imposed upon our memory by future historians. In this respect, it is perhaps proper to conclude with a wish made on November 20, 1782, by Thomas Reid (1739–1803): "In an age like this, of philosophical enquiry, in which the human mind is daily enlightened by the rays of knowledge, I doubt not, but any attempt, however weak, to promote *science*, so essentially necessary to mankind, will be received with liberality, and judged with candor."[9]

Summary

The (extrinsic and fixed) infectious character of tuberculosis is due to a specific, causative microorganism. By contrast, the degree of its (intrinsic and variable) contagious nature depends upon the prospective host, and is determined by the reactability potentials of the tissues contacted by the specific antigens. The

[8] The recent decision of the Public Health Service to discontinue routine chest surveys of the population-at-large, quite reasonable in itself, may have been motivated to a large extent by the national radiation scare. It is regrettable that the prevailing opinion disregards the absence of proved genetic damage after sixty years of liberal use of diagnostic roentgenography, and manifests anxiety when facing an hypothetical danger, the existence of which is assumed by extrapolation to mankind of experiments conducted on insects and low mammals. According to Gopal-Ayengar, as quoted by Hodges (177), natives who inhabit the monazite beaches of Travancore in South India have lived for untold generations under the influence of a relatively elevated radioactive background, equivalent to 20 to 105 r for an accumulated thirty-year gonadal dose, without revealing any genetic or other impairment referable to this radioactivity.

[9] This constructive final quotation was selected in preference to the vitriolic comment by the cynical Mencken: "Human beings never welcome the news that something they have long cherished is untrue: they almost always reply to that news by reviling its promulgator."

[10] This is the summary of the entire article, of which Parts I, II, and III have been published in the two preceding issues of the Review.

magnitude of possible reactability in a given individual ranges from susceptibility (maximally sensitizable) to insusceptibility (insensitizable), with transitional situations along the entire scale. The modification of the reactability potential of a given individual (in function of age and intercurrent events), perhaps by way of altered secretion of corticosteroid hormones, is also contemplated.

Tuberculosis rates follow the trajectory of an asymmetric wave (a shorter ascent and a longer, exponential descent) which is the result of a gradual increase in the average immunity of the population considered, due to a natural weeding-out of reactable individuals. There are successive (not synchronous) peaks of mortality, morbidity, "good chronics," inactive cases, contacts, et cetera among the population studied. The progress of the wave (rise of the immunity level) causes a continuous change in many aspects of the tuberculosis phenomenon. For instance, it alters the proportion of the various clinical types of tuberculosis; it lengthens the average survival time after onset of the illness; and—generally speaking—it tends toward the emancipation of tuberculosis from extraneous (such as seasonal) influences. The speed with which the wave progresses depends on the degree of urbanization of the afflicted population.

Tuberculosis had existed in America prior to its colonization by Europeans, but the disease remained of limited numerical significance until the middle of the eighteenth century. The *first* (Eastern or "English") peak of tuberculosis mortality in North America occurred around 1800 in the large cities along the Atlantic coast, and involved mainly the Anglo-Saxon population. The *second* (Northern, Midwestern, or "German-Irish") peak took place before 1860 within a radius of about five hundred miles around Chicago, and embraced a population of predominantly German and Scandinavian origin. At about the same time, spikes of tuberculosis mortality in some of the large Eastern ports (especially Boston) were caused by Irish immigrants. The *third* (Southern or "Negro") peak appeared around 1880 in southern cities, and resulted from the acute urbanization of the Negroes emancipated after the Civil War. The *fourth* (Southwestern, Far Western, or "Indian") peak occurred prior to 1910 in New Mexico, Arizona, Texas, and California, and was caused by high death rates among a population of Indian origin (both North American and Mexican), the latter known to have a large proportion of Central American Indian ancestry.

The after-effects of this latest peak are displayed in the absolutely and comparatively higher mortality from tuberculosis in the southwestern states. The absence of peaks related to the immigration of other racial stocks is due to the fact that, at the time of their arrival, they were with few exceptions numerically insufficient to outnumber the proportionally high immunity of the local population (Negroes moving North after 1890, eastern and southern Europeans arriving in the metropolitan areas after 1900, Chinese and Japanese reaching the West Coast, displaced persons coming to the United States after World War II). At the most, these immigrants caused a local "overlay," i.e., a higher than otherwise expected tuberculosis mortality.

While the rural areas surrounding the metropolitan peaks trailed the respective

center by twenty to sixty years, improved transportation facilities, especially the automobile, have resulted in a more homogenous urbanization, and consequently in a faster reduction of the tuberculosis death rate. Analysis by age and sex reveals that, at the beginning of the second half of the twentieth century, the population of the United States is well advanced in the endemic stage of its tuberculosis cycle. This disease will hardly ever disappear completely, but it is expected to cease to be a public health problem, and before the end of this century it may become so rare in the United States as to constitute a medical curiosity.

Emphasis is placed on the "change of reactability," which often occurs in relation with a change in environment, and is believed to have a psychosomatic component, acting by way of stress over hormonal channels. This mechanism may represent the most damaging part of the *urbanization* process, even though so-called "social factors" have often been incriminated instead, when a group entered an acute stage of tuberculization.

The decrease in the incidence of, and mortality from, tuberculosis is the result of the natural selection of those susceptible to the specific antigens, i.e., those with high levels of reactability. Since it is inadmissible to decide who shall be subjected to the test of contamination, it appears indicated that the existing procedure of making reasonable efforts toward the detection, isolation, and treatment of bacilliferous individuals should be continued. In view of the expected further increase in the number of former tuberculous patients, as well as in their survival time, special emphasis must be placed on the development of rehabilitation and after-care. In any event, it is imperative, both in the interest of science and for an accurate perspective, to acquire an adequate insight into the causal relationships of the various factors with the tuberculosis phenomenon.

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Case Reports

PULMONARY INFECTION WITH ALLESCHERIA BOYDII[1, 2]

Report of a Fatal Case

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INTRODUCTION

The fungus, *Allescheria boydii*, is the perfect stage of the imperfect fungus, *Monosporium apiospermum* (1). This fungus is a known cause of maduromycosis. In 1955, Creitz and Harris (2) reported in this journal a case from which *A. boydii* was repeatedly cultured from the sputum. The present report deals with the subsequent course of this case.

CASE REPORT

A 56-year-old Spanish-American farmer had had a long period of hospitalization and chemotherapy for tuberculosis and for chronic suppurative pneumonia with multiple abscesses. The patient was subsequently found to be infected with *A. boydii* and, in February, 1954, was transferred to the Denver Veterans Administration Hospital for further investigation and therapy.

At this hospital, roentgenographic studies of the chest (figure 1) showed no essential changes when compared with films from the former hospitalization. Repeated chest films showed no changes throughout the period of observation prior to surgery. Intradermal tests with coccidioidin, histoplasmin, and first- and second-strength PPD were negative. Smears and cultures for acid-fast bacilli were negative on twelve occasions. The impression of pulmonary mycosis was substantiated by the culture of *A. boydii* on twelve consecutive sputum samples. With the laboratory report that the fungus was inhibited by chloramphenicol, treatment with 500 mg. of this drug every eight hours was begun. A slight clearing and a decrease in volume of sputum production were noted. A previously noted occasional afternoon temperature elevation to 100.4° F. disappeared promptly. Although the patient felt better generally, he continued to have a poor appetite and failed to gain weight. During the second week of chloramphenicol therapy, the daily sputum cultures became negative for *A. boydii* and remained so for about ten days. When the sputum cultures again became positive for the fungus, 112 mg. of 2-hydroxy-stilbamidine every other day were added to the regimen. This resulted in no signs of improvement. During the third week of the multiple-drug therapy, the sputum again became negative for *A. boydii* but reverted to positive within ten days. The blood urea nitrogen had become progressively elevated from 15.7 to 24.6 mg. per 100 ml., and drug therapy was discontinued. Within forty-eight hours, the patient felt worse and began to have afternoon temperature of 100.4° to 100.8° F. The reinstitution of chloramphenicol therapy again controlled the fever. The addition of 112 mg. of 2-hydroxystilbamidine intravenously each morning for three days and then 225 mg. daily for ten days was without effect on the clinical, roentgenographic, or mycologic status. The blood urea nitrogen again rose to 24 mg. per 100 ml. and, consequently, treatment with stilbamidine was discontinued.

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[1] From the Laboratory and Chest Services, Veterans Administration Hospital, Denver, Colorado.

[2] Presented in part at the Sixteenth Conference on the Chemotherapy of Tuberculosis, St. Louis, Missouri, February, 1957.

[3] Excellent photographs of these colonies are in the article by Creitz and Harris (2).

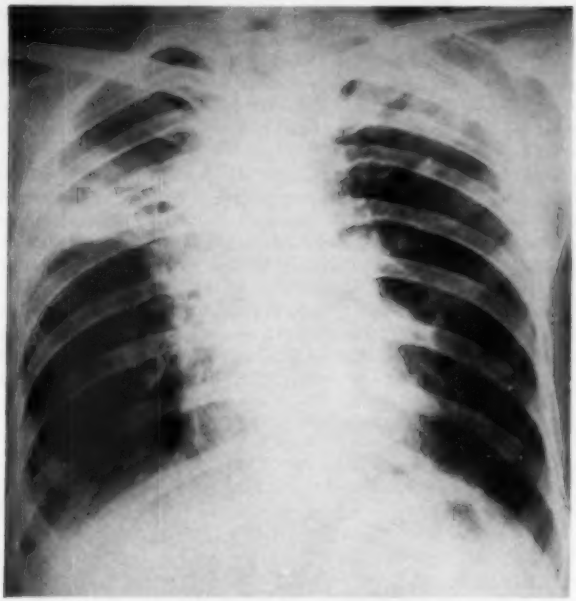

FIG. 1. Postero-anterior chest film which reveals widespread parenchymal infiltrations, markedly widened mediastinum, and bilateral cavitation.

It had become apparent that the patient's course was one of continued deterioration; and the general opinion of the staff was that, if the case was to be salvaged, the abscess had to be resected despite the poor condition of the patient. On June 6, 1954, the patient underwent a right upper and middle lobectomy. Extensive dense pleural adhesions were noted at the operation. The postoperative sputum cultures were persistently positive for the fungus. The right lower lobe failed to expand properly, and the patient developed a hydropneumothorax on that side. The subsequent clinical course was progressively worse, and the patient died twenty-four days after surgery. The opinion of the attending staff was that the main factor immediately contributing to the patient's death was pulmonary insufficiency caused by a bilateral inflammatory process and a poorly functioning right lung following resection of the upper and middle lobes.

Mycologic and Pathologic Findings

Mycology: The imperfect stage of the fungus was readily cultured from the sputum on Sabouraud and Thompson media. Typical colonies with the characteristic pyriform conidia[2] appeared within two or three days at either 20° or 37° C. incubation. The perithecia[3] of the perfect stage developed on subculture to potato dextrose agar. Microscopic examination of wet mounts and stained smears of the sputum revealed no structures which could definitely be identified as the fungus. Drug-susceptibility tests using the agar-plate dilution method revealed the fungus to be 75 per cent inhibited by 20 γ of chloramphenicol per ml. and 100 per cent inhibited by 100 γ of chloramphenicol. However, the fungus cultured from the sputum after three weeks of therapy with chloramphenicol grew luxuriantly in the presence of 100 γ of the drug per ml. Inhibition of the fungus was not shown by 5 γ of 2-hydroxy-stilbamidine per ml., but moderate inhibition was manifested by 10 γ per ml., although a few resistant variants grew in the presence of 200 γ of this drug per ml.

Pathology of resected lung: The resected lung showed considerable pleural thickening with a few small, firm, anthracotic-appearing lymph nodes in its hilar portion. On section, the upper portion of the lobe appeared densely fibrotic while the lower portion of the lobe contained a large multiloculated cavity which measured approximately 7 by 4 by 3 cm. The bronchi were opened in their entirety and appeared to have thick walls; the lowest ones appeared to communicate directly with the cavity. Satisfactory cultures were not obtained from the resected lung.

Multiple sections from the lung showed a generalized inflammatory infiltration, marked fibrosis obliterating much of the normal alveolar pattern which, however, persisted in areas. The inflammatory cells were mostly of the chronic type and there were associated areas of hemorrhage and necrosis. Areas of regenerating alveoli were apparent, with characteristic cuboidal epithelium. In addition, an occasional well-formed small epithelioid tubercle was seen. The major lesion of the lung appeared to be of this epithelioid nature, consisting of cavities with convoluted walls lined by concentrations of epithelioid cells arranged in parallel fashion. In some areas, this epithelioid structure was seen in an endobronchial location. Much inflammatory infiltration with many neutrophils was present. Some of the concentrations of epithelioid cells appeared to form a membrane about small abscess cavi-

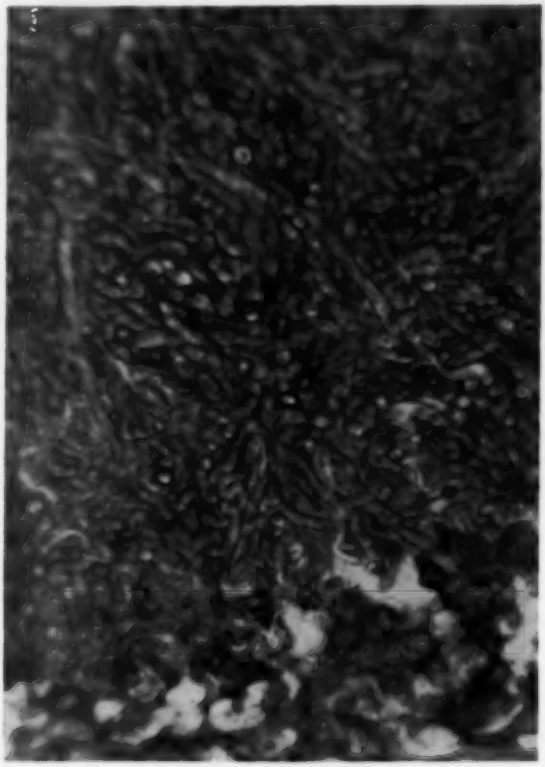

FIG. 2. Section of cavity in resected lung. Mycelial clumps composed of branching septate hyphae with spores are seen in the abscess cavity. (PAS stain, 500 ×)

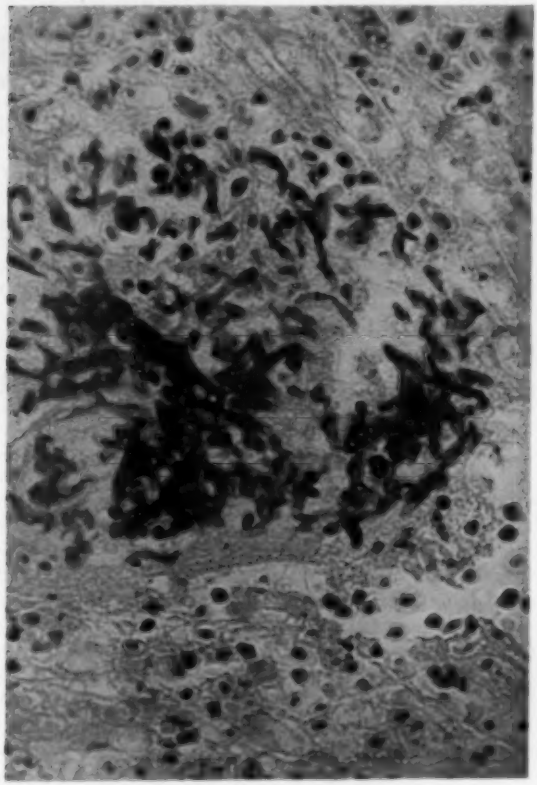

FIG. 3. Mycelial fragments and spores are seen within the wall of the abscess. (Gomori methenamine silver nitrate stain, 400 ×)

ties. Although these cells were readily recognizable, their pattern of arrangement was unlike any observed in the common granulomas. Mycelial clumps composed of branching septate hyphae with spores were seen in the necrotic lining and apparently also in the wall of the abscess cavity (figures 2, 3).

Post-mortem findings: The right pleural cavity contained approximately 2,000 ml. of thick yellow-gray purulent fluid. The remainder of the lung was completely collapsed and formed a small, firm, triangular mass continuous with the mediastinum in the inferomedial portion of the pleural cavity. The cavity was covered by a thick overlay of a yellow-gray plastic exudate. The left pleural cavity was completely obliterated by dense fibrous adhesions between the visceral and parietal pleurae. The lung was removed with difficulty because of pleural thickening by dense fibrous tissue.

The left lung weighed 1,090 gm. The pleural surface was ragged and shaggy due to remnants of fibrous adhesions. At the extreme apex there was a cavity approximately 5 cm. in diameter. This cavity was extremely thin-walled and was located just beneath the pleural surface in the superior portion of the apex; in its other aspects, the cavity was surrounded by a relatively thick fibrous capsule and did not communicate with any bronchial branches.

A yellow-brown plastic exudate was adherent to one area of the lining of the cavity. The contents of the cavity consisted of approximately 2 ml. of thin, turbid, yellow-gray fluid. Wet mounts of the fluid revealed the characteristic pyriform conidia and hyphae in abundance. Cultures of this material gave a luxuriant growth of *A. boydii*. Acid-fast stains and cultures were negative for tubercle bacilli.

In the vicinity of this large cavity was a much smaller one, less than 1 cm. in diameter, surrounded by dense, pearly, rubbery scar tissue. The remainder of the lung showed no gross evidence of consolidation or other lesions, but was congested and edematous. No further extension of the lesion of the upper lobe could be demonstrated. The left lung was removed with considerable difficulty. It was completely encapsulated by a very dense and thick fibrosis of the pleura. The parenchyma itself was airless, rubbery, and dark red-gray with obvious atelectasis. No gross lesions could be demonstrated throughout the parenchyma. The mediastinum contained a number of firm anthracotic lymph nodes, often collected in confluent masses surrounded by fibrous scarring. Multiple sections from the region of the cavity in the left upper lobe showed a lesion similar to the one found in the resected lung, although the fungus was not found in these sections.

Other than the findings in the lungs and pleurae, the gross pathologic findings were not remarkable. The heart was only slightly enlarged. Microscopically, there was evidence of hyperemia in the liver, spleen, kidneys, and adrenals.

Discussion

To the knowledge of the present writers, this is the first recorded case of pulmonary infection with *A. boydii*. Drouhet (3) mentioned the repeated isolation of *Monosporium apiospermum* from sputum in a case of pulmonary mycetoma in France. However, it has not been possible to obtain the details of this case.

The exact relationship of the fungus to the lung lesion in the present case is difficult to assess. The failure of stains and cultures to reveal any other etiologic agent lends support to the possibility of a primary infection, although the possibility that this fungus was a secondary invader could not be completely excluded. *A. boydii* has been shown to occur in soil (4–6), polluted water, and sewage (7). However, infection by inhalation of the fungus is not known to occur and, although septicemia has been reported in one instance (4), the absence of a primary skin lesion in the present case would seem to preclude that possibility also. Consequently, the question of the route by which this fungus reached the lung remains unanswerable in the present case.

An interesting and unexpected aspect of the case was the subjective and objective signs of therapeutic effect with chloramphenicol. Unfortunately, the fungus was able to develop resistance rapidly to the drug. This development of resistance was correlated with *in vitro* drug-susceptibility test results. It is possible, however, that chloramphenicol might be more effective in less extensive or more superficial infections with *A. boydii*.

Summary

A fatal case of pulmonary infection with *Allescheria boydii* is presented. The gross and microscopic pathology of the lung and the relationship of the fungus to the lung lesion are described.

Sumario

Infección Pulmonar por Allescheria Boydii: Presentación de un Caso Letal

Preséntase un caso letal de infección pulmonar por *Allescheria boydii*. Descríbese la histopatología macro y microscópica del pulmón. Se discute la relación del hongo con la lesión pulmonar.

RESUME

Infection pulmonaire à Allescheria boydii: Rapport sur un cas mortel

Présentation d'un cas d'infection pulmonaire à *Allescheria boydii* à issue fatale. Les lésions macroscopiques et histologiques du poumon sont décrites. La corrélation entre le fungus et la lésion pulmonaire est commentée.

Acknowledgment

The photographs were prepared by Mr. Jack Fason of the Medical Illustration Laboratory of this hospital.

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DIFFUSE INTERSTITIAL PULMONARY FIBROSIS (HAMMAN-RICH SYNDROME)[1]

Report of Three Cases

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(Received for publication March 24, 1958)

Introduction

In 1944 (1), Hamman and Rich listed pathologic peculiarities of a condition first described by them in 1935 (2). They designated the condition "acute diffuse interstitial fibrosis of the lungs" and presented it as a clinical and pathologic entity characterized by progressive, diffuse fibrosis of the alveolar walls. The adjective "progressive" referred to the fact that all stages of the process, from the acute inflammatory phase to complete fibrosis, could be found in histologic sections of the lungs, so that all lobes of both lungs were diffusely involved with lesions in different stages of development. Since then, additional aspects have been noted, and the condition has become known by the broadened terminology of "Hamman-Rich syndrome." Less than 65 cases have been reported, but the entity is fairly well known and it is likely that many cases have been unreported.

Review of the Literature

Not all of the reported cases are similar as to diagnosis and classification. For instance, Grant and associates (3), in reporting 39 collected cases, included cases of Potter and Gerber (4), Golden and Tullis (5), and Katz and Auerbach (6). But Peabody and co-workers (7) reject the case of Katz and Auerbach. Heppleston (8) believed that the cases of Golden and Tullis more closely resembled primary atypical pneumonia. Potter and Gerber report that lesions with features similar to their own case are noted in atypical or viral pneumonia. Golden (9) was of the opinion that one of the original cases described by Hamman and Rich represented interstitial pneumonitis. Cox and Kohl (10) believed that the process represented a series of attacks of interstitial pneumonitis resembling atypical pneumonia, but with fibrosis following each attack. They proposed the term "diffuse fibrosing interstitial pneumonitis." Others (5, 11, 12) agree essentially with this concept.

Reference to most of the purported cases (1–8; 10–25; 30–32) gives a comprehensive review of the subject and reveals the constant and outstanding feature present in all cases to be an interstitial fibrous tissue proliferation. This was stressed in the original descriptions (1, 2) and in the recent past (27, 29). Other features reported, however, are inconstant and varying, and some may not even be part of the condition per se, possibly being produced or influenced by treatment, e.g., with corticosteroids, or other factors not yet elucidated.

At present, the current pathologic terminology of "diffuse interstitial pulmonary fibrosis" is most apt, descriptive, and simple, and should be used for purposes of clarity and ease of indexing. Eventually, as physicians have experiences with more cases and as other features become better understood, further classification may develop.

In this report, 3 case histories are presented which reveal interesting facets of the Hamman-Rich syndrome.

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Report of Cases

Case 1. A 38-year-old white male was admitted to the hospital in July, 1953. He had had progressive shortness of breath for two and a half years and a mild nonproductive cough. There was no history of febrile or acute illness. He had worked as a salesman in West Texas, New Mexico, and Colorado, and was unaware of exposure to any noxious agents.

Physical examination showed considerable clubbing and cyanosis of the hands and feet and obvious shortness of breath on minimal exertion. Scattered crackling rales were heard throughout both lung fields, especially in the lower portions. A chest roentgenogram (figure 1) showed a diffuse, somewhat granular infiltrate, more dense in both lower lobes, with extension towards the apices, especially on the right. An electrocardiogram showed right ventricular strain. Blood pressure was normal. Urinalysis, blood urea nitrogen, serologic tests for syphilis, carbon dioxide combining power, total protein with albumin-globulin fractions, serum calcium, alkaline phosphatase, and blood chlorides were within normal limits. A bronchoscopy showed no significant abnormalities. A scalene lymph node biopsy revealed normal findings. Complement-fixation studies and skin tests for *Histoplasma capsulatum* and *Coccidioides immitis* were negative; tuberculin skin tests were negative. A complete blood count was normal except for an 8 to 10 per cent eosinophilia on several occasions. Pulmonary ventilatory studies revealed a severe restrictive defect. Cardiac catheterization data revealed a diffusion defect and early pulmonary hypertension.

Lung biopsy: A lung biopsy showed replacement of alveolar tissue by dense, fibrocollagenous tissue, in which small collections of lymphocytes and plasma cells were scattered. There were a few air spaces in the section, mostly bronchioles, plus a few other air spaces lined by cuboidal epithelium containing macrophages, with foamy cytoplasm, a few polymorphonuclear leukocytes, and occasionally a giant cell. Large amounts of smooth muscle were also present (figure 2). The small arteries showed minimal sclerosis. The replacement of lung tissue by fibrosis and the lack of marked inflammatory reaction were striking features.

After his discharge, the patient received various symptomatic medications, but became progressively more dyspneic. Occasionally he would expectorate a small amount of sputum, sometimes slightly purulent.

His last admission was on February 9, 1955. Significant physical findings were unchanged. A chest roentgenogram revealed progression on comparison with previous films. Laboratory examinations again were normal.

Because of the progression of symptoms, cortisone therapy was instituted on March 9: 200 mg. daily for three days; then 150 mg. daily for three days; and later 100 mg. daily thereafter. Prompt improvement ensued. On April 1, 1955, the patient noticed increased dyspnea and minimal hemoptysis. Physical findings and roentgenograms revealed pneumonitis in the left upper lobe. The patient was treated with oxygen, bronchodilators, antimicrobials, expectorants, and steam inhalations. Despite these measures, he died on April 3, 1955. The death was considered typical of asphyxia.

Post-mortem findings: At autopsy the right lung weighed 1,000 gm., the left, 800 gm., and both were markedly firm, with minimal crepitus. The pleura over all surfaces was smooth and glistening, except for a few isolated areas over the right lung, where there were shaggy fibrinous adhesions. Beneath the pleura, the lobes of both lungs showed many minute emphysematous blebs interspersed between an abundance of fibrotic material. The usual gray, pigmented, mottled appearance was absent. Bronchi showed no points of ulcer or obstruction; pulmonary arteries and veins were normal. The cut surface revealed loss of alveolar architectural markings, being replaced by abundant fibrous tissue and minute cystic areas. A moderate amount of frothy pink edematous fluid was expressed from the dependent portions of all lobes. Hilar lymph nodes were moderately enlarged, and cut surfaces revealed small fibrotic areas throughout.

Microscopically, the interalveolar septa, interstitial tissue, and alveolar walls showed moderate-to-marked thickening due to edema, granulation tissue with chronic inflammatory cells, and fibrous tissue (figure 3). There was marked distortion of the architecture, and fragmentation of the epithelioid type of cells appeared singularly and in clumps. Many areas

Fig. 1. *Case 1.* (Left) Admission chest roentgenogram. Symptoms had been present two and a half years. (Center) Follow-up roentgenogram showing progression; patient was increasingly dyspneic. (Right) Roentgenogram obtained during final admission, thirteen days before death, and twelve days after institution of corticosteroid therapy.

showed intercommunicating alveolar spaces with squamous metaplasia. Fibrin hyalin membranes and Masson's bodies were seen only occasionally. Small foci of polymorphonuclear leukocytes, cellular debris, and necrotic material were found within the alveolar spaces and bronchi. The left apical area showed marked granulation tissue. In the lower lobes, connective tissue was more dense in appearance. When granulation tissue was marked, accompanying hyperemia and hemorrhage were identified. Cystic dilatation

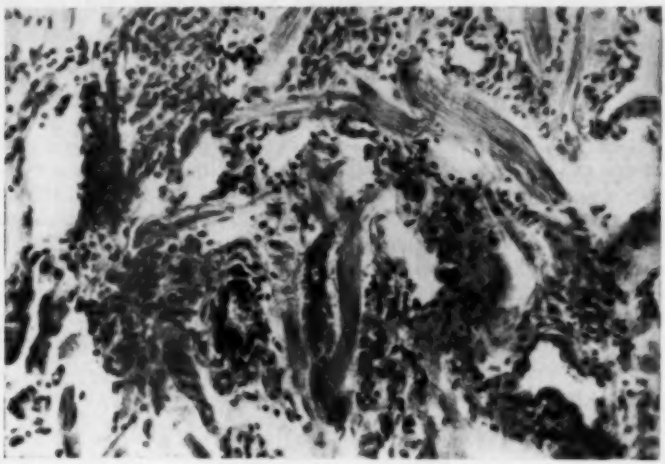

FIG. 2. *Case 1.* Lung biopsy (× 200) showing the large amount of fibrous tissue and lack of marked inflammatory reaction. Note the pronounced smooth muscle proliferation.

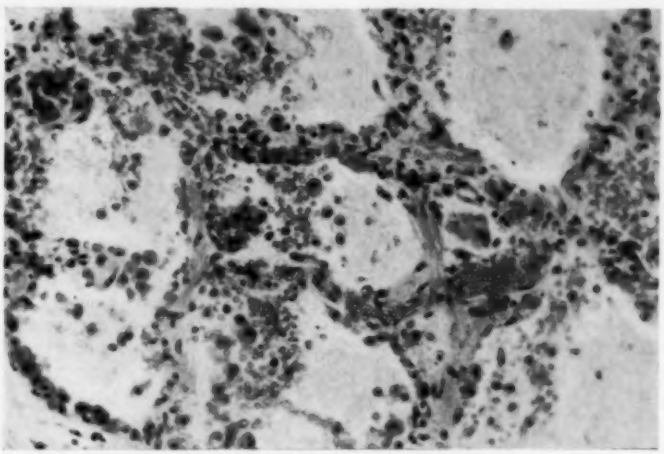

FIG. 3. *Case 1.* Autopsy section of lung (× 200) showing increased prominence of vascular channels and abundant fibrous tissue in interstitial tissues. Smooth muscle was not prominent in autopsy sections of the lungs.

and hypertrophy of bronchial musculature were seen, and many bronchiolar spaces showed papilliferous formations of proliferating columnar and cuboidal cells. Giant cells, granulomatous reaction, or inclusion bodies could not be identified. One of the most striking features seen in all sections was the atypical cells lining the alveolar spaces. Pleura in all sections was thickened, hyperemic, and appeared continuous with the subpleural parenchyma. Some of the small arteries and arterioles showed secondary atheromatous changes.

Other pertinent autopsy findings showed that the heart weighed 275 gm.; the right ventricle was 2 mm. thick, and the left 9 mm. thick. There was marked fatty metamorphosis of the liver.

Comment: The nature and location of the fibrous tissue elements in specimens of lung examined by biopsy and autopsy coincide with the original description of Hamman and Rich.

The marked proliferation of smooth muscle in the biopsy specimen is similar to the case of Harris and associates (17) and represents one of the few instances wherein pronounced muscular hyperplasia has been recorded. Liebow (26) reviewed the subject of muscular hypertrophy in the lungs of patients with chronic pulmonary disease and concluded that a remarkable hypertrophy and hyperplasia of muscle occurs in many types of chronic pulmonary disease. There must be other cases of the Hamman-Rich syndrome wherein smooth muscle hypertrophy has been observed but not mentioned in pathologic descriptions.

This patient represents the twentieth reported case of the Hamman-Rich syndrome treated with corticosteroids (7, 15–22, 30–32). The effect of this therapy is difficult to assess, since treatment had been instituted only three and a half weeks prior to death.

Case 2. The patient was a 61-year-old white male truck driver, admitted to the hospital on December 21, 1954. Increasing exertional dyspnea had incapacitated him for three years. He dated onset of his illness to 1945, at which time he had had marked increase in weight, a dry hacking cough, shortness of breath on exertion and at rest, paroxysmal nocturnal dyspnea, and orthopnea. For six or seven months, he had had swelling of the feet, ankles, and hands intermittently during the day, receding overnight; night sweats; a cough productive of about a teaspoonful of yellow-gray sputum daily; and occasional wheezing at night. There was no chest pain or fever. On a reducing diet the patient's weight dropped from 247 to 197 pounds, after which he felt remarkably improved and returned to work, with only slight persistence of shortness of breath. Intermittent swelling of the feet and ankles continued when he stood too long.

In the latter part of 1946, diabetes mellitus was diagnosed, and the patient was placed on 40 units of isophane (NPH) insulin daily and a 2,000-calorie diet. In 1949 he suddenly lost use of the left side of his body for about one and a half hours, but gradually regained use of the extremities. In the two years before final admission, he began having "smothering spells" at night, relieved by sitting up and by nitroglycerin.

Significant physical findings were: obesity, pallor, clubbing of the fingers and toes, grade-one pitting edema of lower extremities, numerous crepitant rales in both lungs, and neurologic findings of diminished sensation in the left thigh and lateral aspects of the left leg, numbness of the toes, slightly decreased vibratory sensation, and equal deep tendon reflexes.

Hemoglobin was 12 gm. per 100 ml.; the erythrocyte count, 3.5 million per cu. mm. Leukocytes were 1,950 per cu. mm. and the differential leukocyte count was normal. The platelet count was 50,000 per cu. mm. A reticulocyte count was 2.6 per cent of erythrocytes per cu. mm. Bleeding time was normal, coagulation time, venous blood (Lee-White method) was thirteen minutes. Mean corpuscular hemoglobin concentration of erythrocytes was 36 gm. per 100 ml. of packed erythrocytes; the mean corpuscular volume of erythrocytes was 96 cubic microns. Prothrombin time was 17 per cent of control; the Van den Bergh test was normal; four-day fecal urobilinogen was 105 Ehrlich units in the sample of 310 gm.; urine

urobilinogen showed 0.42 Ehrlich units in a two-hour afternoon specimen. Urinalysis was normal. Coomb's test, serologic tests for syphilis, stool examination for occult blood, and gastric washings for acid-fast bacilli were negative. Skin tests with Old Tuberculin, histoplasmin, and coccidioidin (each in 1:100 dilution) were negative. Blood urea nitrogen, total serum proteins with albumin and globulin determinations, fasting blood sugar, carbon dioxide combining power, serum chlorides, serum sodium and potassium, alkaline phosphatase, and serum uric acid were normal. Agglutination reactions for typhoid fever and brucellosis were negative, and there was no significant titer of cold agglutinins. The total serum cholesterol was 329 mg. per 100 ml.; cholesterol esters were 210 mg. per 100 ml. Serum calcium was 8.9 mg. per 100 ml. The blood sedimentation rate (Wintrobe) was 30 mm. in one hour. Electrocardiograms were diagnostic of old apical myocardial infarction. Chest roentgenograms revealed pulmonary fibrosis with some cystic changes throughout both lung fields.

During hospitalization, the main manifestation of this patient's pulmonary disease was shortness of breath on exertion. Leukopenia and mild anemia persisted, with no obvious explanation. Two bone marrow specimens from different sites showed only erythroid hyperplasia. Reticulocyte counts varied from 2 to 6 per cent and were not affected by administration of vitamin B_{12} or folic acid. Diabetes was generally well controlled.

Shortly after admission, the patient developed acute thrombophlebitis of the right leg and received anticoagulant therapy. Initially he had several attacks of severe angina pectoris, but after six weeks in bed he became relatively free of these episodes. He began to complain of weakness and loss of appetite, and tube feeding was instituted. About four days prior to death, he received about 200 ml. of a blood transfusion which produced a febrile reaction. The next day, another transfusion was started, but he began to hyperventilate and again his temperature rose. On April 3, 1955, he suddenly complained of severe shortness of breath; he began to breathe rapidly, and became cyanotic and died in about ten minutes.

Post-mortem findings: At autopsy, the right lung weighed 750 gm.; the left, 650 gm.; the lungs were markedly firm, with minimal crepitus. Parenchyma of the lobes just beneath the pleura imparted a lobulated appearance similar to that seen in hob-nail liver. At the base of all lobes were small emphysematous blebs. The usual pigmented mottled appearance was replaced by a monotonous tan-gray color except in the dependent portion, where purple discoloration was identified. The bronchi showed no ulceration or obstruction. Pulmonary arteries and veins were free of emboli and thrombi; some atherosclerosis was noted. The cut surface of each lobe imparted resistance similar to that found in the liver. In the dependent portions, frothy pink edematous fluid could be expressed. No areas of necrosis or granulomas were identified. Hilar lymph nodes were enlarged, of normal consistency and, on cut surface, contained normal anthracotic pigment with small fibrotic areas.

Microscopically (figure 4), there were variable amounts of organizing fibrous material in the alveoli, both as hyaline membrane and as material resembling Masson's bodies. The alveolar walls were thickened as a result of tortuous capillaries, fibrous tissue, granulation tissue, and chronic inflammatory cells. Connective tissue completely obliterated the alveolar lumina in many areas. The hyaline membranes in some areas appeared as homogenous, pink-staining bands, and adhered to the inner surface of the alveolar walls; in other areas, there was slight-to-marked organization brought about by granulation tissue which appeared to be coming from the alveolar walls. In some areas, many alveoli appeared as slitlike spaces lined by epithelial cells as a result of epidermalization. Areas of hyperemia and hemorrhage were scattered throughout all fields. In addition, the alveoli contained bizarre-appearing histiocytes with debris within the cytoplasm. Peribronchial and perivascular lymphocytic infiltration was seen. The epithelial lining of some bronchi was desquamated and in some areas was replaced by metaplastic squamous cells. Bronchial lumina and some of the alveolar spaces contained focal areas of cellular debris and polymorphonuclear leukocytes. The small arteries and arterioles showed moderate-to-marked

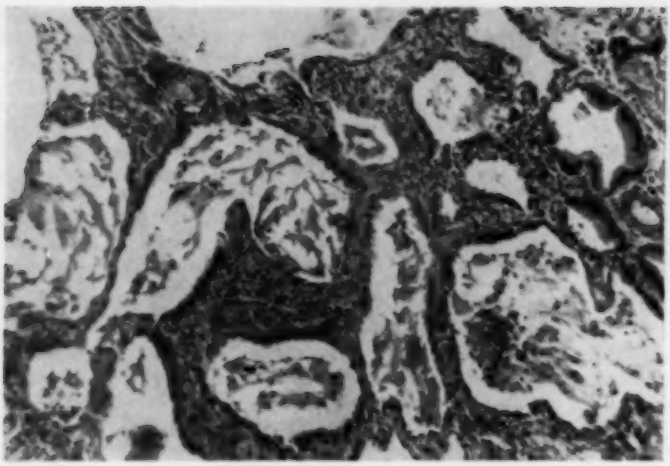

FIG. 4. *Case 2.* Autopsy section of the lung (× 200) showing the alveolar walls markedly thickened by fibrous tissue proliferation. Note the cuboidal epithelial lining cells of the alveolar walls.

intimal fibrosis. Some veins showed organizing thrombi. In all representative sections, the pleura was completely fused and continuous with the parenchyma.

Other pertinent findings showed atherosclerosis of the coronary arteries with occlusion of the left anterior descending branch, myocardial fibrosis, calcification of the aortic valve, atherosclerosis of the aorta, and arteriolonephrosclerosis.

Comment: The pathologic description in this case allows some room for differences of opinion in regard to classification. It is similar to the case of Cox and Kohl (10) and would seem to fit in with their concept of interstitial pneumonitis resembling atypical pneumonia and with accompanying interstitial fibrosis. However, the distribution and nature of the fibrosis are thought to be generally in keeping with Hamman and Rich's original description.

Case 3. The patient was a 59-year-old white male whose final admission to the hospital was on January 25, 1957. He had been hospitalized several times previously. In 1947, when a cholecystectomy was done, he was noted to have pulmonary fibrosis and hypertrophic pulmonary osteoarthropathy, and he gave a history of progressive shortness of breath and chronic cough since 1942, when he inhaled some coral dust while stationed in Bermuda. Physical examination in 1947 revealed accentuated P-2; some transitory wheezes and rales in the bases, more on the left; and marked clubbing of fingers and toes without obvious cyanosis. Roentgenographic studies of the hands showed early changes consistent with pulmonary osteoarthropathy. Vital capacity was 2.4 liters (56 per cent of predicted). Venous pressure was 40 mm. of water, and arm-to-tongue circulation time was 12 seconds (Decholin®). Electrocardiograms were normal. Hemoglobin was 14 gm. per 100 ml. Sedimentation rate (Wintrobe) was 20 mm. in one hour. The erythrocyte count was 5 million per cu. mm. Differential blood smears were normal. The hematocrit was 46 per cent; the pulse rate during hospitalization varied from 70 to 90 per minute.

The *second admission,* in 1955, was for pain in the left shoulder. Pulmonary symptoms had not changed. Roentgenograms of ankles and knees showed a typical picture of hyper-

trophic pulmonary osteoarthropathy. Hemoglobin was 16.9 gm. per 100 ml.; the erythrocyte sedimentation rate was 14 mm. in one hour. Serologic tests for syphilis were negative. Hematocrit was 50 per cent. A chest roentgenogram showed fibrosis without much change. Blood pressure was normal, pulse 80, weight 190 pounds. The patient was afebrile. There was enlargement of the fingertips, and mild cyanosis of the lips was noted.

The *third admission* was early in 1956, with complaints of increased cough, shortness of breath, and vomiting, of about three days' duration. The patient was acutely ill and in respiratory distress. There was cyanosis of lips and hands. Fine rales were heard throughout both lung fields except at the apices, and were most marked posteriorly. His weight was 175 pounds. He was afebrile; his pulse ranged from 80 to 90 per minute. Significant laboratory findings were: hemoglobin, 15.5 gm. per 100 ml.; erythrocyte sedimentation rate, 37 mm.; hematocrit, 49 per cent; leukocyte count, 16,000 per cu. mm., with normal differential smear. Carbon dioxide combining power and blood urea were normal. A chest roentgenogram showed a superimposed pneumonitis in the right lung. An electrocardiogram, compared with a tracing from 1947, showed a shift in electrical axis with diffuse T-wave negativity in anterior V leads; incomplete right bundle branch block; no evidence of acute cor pulmonale. The patient was treated with antimicrobials, oxygen, and expectorants; he rapidly improved. In two weeks, chest roentgenograms showed clearing of the pneumonitis, but the fibrosis was unchanged. Following this, the patient was generally fairly well except for a cough and slight expectoration of mucoid sputum and the usual shortness of breath. At discharge, he could walk about a block downhill without much difficulty.

Follow-up observations: On examination in the outpatient department in September, 1956, dyspnea had increased and the patient could walk only a few feet without shortness of breath. Laboratory examinations revealed a leukocyte count of 11,000 per cu. mm., with a normal differential blood smear except for 6 per cent eosinophils. Hemoglobin was 17.6 gm. per 100 ml. and hematocrit was 52 per cent. The erythrocyte count was 6.8 million per cu. mm.

The *final hospital admission* was on January 25, 1957. The patient gave a history of increasing shortness of breath and swelling of the feet and legs. The slightest exertion produced severe dyspnea. He had no chest pain and no discomfort in his joints. He had occasional wheezing. There was no history of chills or fever. Physical examination revealed normal temperature and blood pressure; pulse, 120 per minute; the respiratory rate varied from 30 to 40 per minute. There was marked cyanosis of lips and fingernail beds, markedly deepening with slight exertion, improving after ten to fifteen minutes of rest. Examination of the chest showed limited expansion bilaterally, resonant percussion note, and no change in tactile fremitus. Breath sounds were fairly well heard over the upper chest anteriorly and posteriorly. Anteriorly over the lower portions were fine, moist, inspiratory rales. Posteriorly over the lower third were fine and moderate moist rales on inspiration and expiration. There were a few scattered wheezes. Examination of the heart revealed marked accentuation of P-2 and an occasional premature ventricular contraction. The liver and spleen were not palpable. Grade-three pitting edema of the lower extremities and marked clubbing of the fingers were noted.

The leukocyte count was normal, with normal differential smear; the erythrocyte count was 7.1 million per cu. mm. Hemoglobin was 19.8 gm. per 100 ml.; hematocrit, 59 per cent; erythrocyte sedimentation rate (Wintrobe), 14 mm. in one hour. A urinalysis showed grade-two albumin and 1.020 specific gravity. Urea nitrogen was 19 mg. per 100 ml. The carbon dioxide combining power was 22.7 mEq. per liter (50 volumes per cent). Liver function studies revealed a cephalin flocculation of grade two; thymol turbidity was 5.9 units; alkaline phosphatase was 1.4 Bodansky units per 100 ml. Repeat blood studies were unchanged. Other blood chemistries included initial sodium determination of 135 mEq. per liter; potassium 3.7 mEq. per liter. Total serum proteins were 6.8 gm. per 100 ml., with an albumin fraction of 3.6 gm. per 100 ml. Repeat carbon dioxide combining power determinations were never elevated. Sputum examinations were negative for evidence of oil; bacteriologic examination showed a light growth of *Staphylococcus aureus*. An electrocardio-

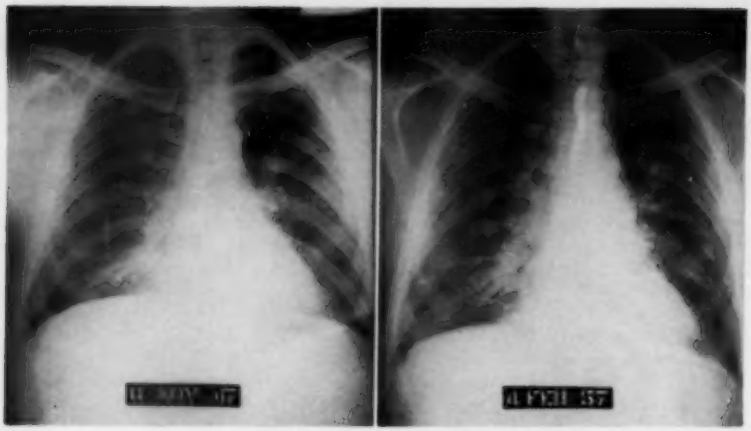

FIG. 5. *Case 3.* (Left) Chest roentgenogram obtained on first admission to McKinney Veterans Administration Hospital. Symptoms had been present about five years. (Right) Roentgenogram obtained about two and a half weeks before death and showing only moderate increase of the infiltration.

gram showed right ventricular hypertrophy and evidence of a right bundle branch block. Venous pressure was 230 mm. of saline.

A roentgenogram of the chest revealed pulmonary fibrosis, the appearance of the lung fields being about the same as in March and September, 1956, but with increased fibrosis compared to earlier films (figure 5). An esophagram was normal, with no evidence of scleroderma.

The patient was given digitalis and antimicrobials, bronchodilators, and one injection of Mercuhydrin®. His weight dropped from 191 pounds, remaining at 165. He was put in an oxygen tent, with prompt decrease of cyanosis. For several days he seemed to be improving, but suddenly he felt worse, had clouding of sensorium, increasing apprehension, and marked cyanosis at rest in the tent. On February 22, he was started on prednisone (Meticorten®) in dosages of 12.5 mg. every six hours. The course was downhill, and the patient died quietly on February 23, 1957.

Post-mortem examination: At autopsy the lungs were larger than normal and weighed 2,240 gm. They failed to show post-mortem collapse and had a moderately firm, nodular surface. In the right apex, a moderate number of fibrous adhesions were present. Cut surfaces were gray-pink and dry. The air spaces were slightly to moderately distended, more marked in both upper lobes, especially at lateral and apical aspects. The bronchial tree was patent, with a smooth wall. Occasionally, branches of the pulmonary artery contained flattened, yellow-orange atheromata within their walls. Peribronchial lymph nodes were unremarkable. In the lateral lower aspect of the left upper lobe, a wedge-shaped, dark red, 4 by 3-cm. area was seen.

Microscopically, multiple sections stained with routine and connective tissue preparations showed the main alteration to be interstitial fibrosis (figures 6 and 7), best seen with the connective tissue preparations when alveolar walls throughout all lobes showed some degree of fibrosis. There was generalized distention of alveoli and air sacs; large numbers of macrophages, some of which were fused to form multinucleated giant cells, were present within alveolar spaces; there was marked vascular congestion, thickening of the walls of the arterioles, mild infiltration by lymphocytes in interstitial areas, and squamous metaplasia of the epithelium of the middle-sized bronchi. There was no evidence of a specific type of inflammatory process, neoplasm, or granulomatous disease.

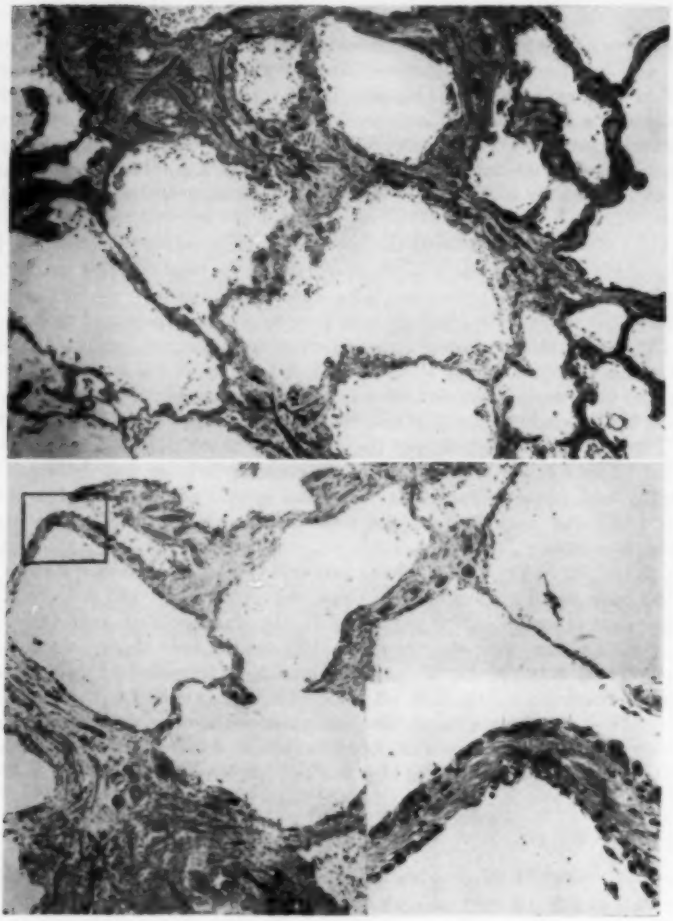

FIG. 6. *Case 3.* (Upper) Autopsy section of the lung (× 30) showing marked interstitial fibrous tissue proliferation.

FIG. 7. *Case 3.* (Lower) Autopsy section of the lung (× 30) showing dilated air spaces and thickening of interalveolar septae. *Inset* (× 280) shows prominent vascular channels, metaplasia of alveolar lining cells, and clearly shows the pronounced fibrous tissue proliferation in the alveolar walls.

Other pertinent findings showed atherosclerosis of the aorta and coronary arteries. The heart weighed 536 gm.; the right ventricular wall was 3 mm. thick; the left, 16 mm. thick. Both ventricular chambers were moderately dilated.

Comment: The fifteen years' duration of symptoms from the time of onset in this patient until death is the longest such period yet reported. In several other reports (5, 7, 18, 19, 30, 32), the duration had varied from five to ten years. Those reports also attest that the term "acute" is certainly not always apropos.

Discussion

In the present report, the first 2 patients died abruptly from a terminal purulent process. One had received corticosteroid therapy which had not been withdrawn; the other never received corticosteroid therapy. In 1953, Peabody and associates (7) reported cases of the Hamman-Rich syndrome in which abrupt death followed withdrawal of corticosteroid therapy. Their patients, likewise, died from a terminal purulent process. The experience of the present writer suggests that perhaps it is not only the withdrawal of steroid therapy which is dangerous, but also the presence of uncontrolled secondary infection.

The exact place of corticosteroid therapy in the Hamman-Rich syndrome is not yet established, but corticosteroids hold promise of being the most effective treatment that can be offered, provided such treatment is instituted before too much old fibrous tissue has formed. In most instances in which patients have received corticosteroid therapy (7, 15–22, 30–33), treatment was started during the terminal phase and continued from a few days to only a month or two. In 4 cases (15–17, 33), diagnosis was established soon after the onset of symptoms, and treatment was instituted promptly. Three of these patients are still living. The fourth patient (17) received definite benefit from corticosteroid therapy for more than two years, but stopped the medication herself about a year before death. While the number involved is small, it is encouraging to note that prolonged steroid therapy has been of benefit in at least 4 cases of this generally fatal process. It is important to note further that early diagnosis and prompt institution of therapy were significant factors in those cases.

Until the publication of a recent report (30) with two of the patients still living, whose symptoms have lasted for five and ten years, respectively, and who have not received corticosteroid therapy, no *living* patients with the Hamman-Rich syndrome were reported except the three early-diagnosed and early-treated cases above. In all other published reports the mortality has been 100 per cent; most patients died within a few days to several weeks, but a few (5, 7, 18, 19, 32) lived as long as five to nine years. Care must be exercised that this recent information is not construed to mean that patients do as well without treatment. With the present knowledge of this syndrome and its treatment, the fact that two patients are still living after five and ten years without definitive treatment attests only to the chronicity of the process in those two patients.

Summary

Less than 65 cases of diffuse interstitial pulmonary fibrosis (Hamman-Rich syndrome) have been reported. All reported cases have the common fundamental feature of interstitial fibrous tissue proliferation, as described by the original authors. Divergent opinions arise from the stressing of other features, some of which may not be part of the condition per se.

Three case histories are reported. In one case, the duration from onset of symptoms until death was fifteen years, representing the longest duration reported. Another patient was treated with corticosteroids and represents the twentieth reported case of a patient so treated. As in most other reported cases of patients similarly treated, therapy was of short duration (three and one-half weeks) and difficult to evaluate. In this same case there was pronounced muscular hyperplasia, representing one of the few instances wherein smooth-muscle proliferation has been reported as being so prominent.

The place of corticosteroid therapy has not yet been established, but prompt corticosteroid therapy is strongly indicated if the diagnosis is made early. Three of 4 of the patients are still living, representing 75 per cent survival in this group, while only 3 per cent of all other patients reported upon are living.

Sumario

Fibrosis Pulmonar Intersticial Difusa (Síndrome de Hamman-Rich): Presentación de Tres Casos

No llegan a 65 los casos de fibrosis pulmonar intersticial difusa (síndrome de Hamman-Rich) descritos hasta ahora. Todos los descritos poseen en común la característica fundamental de proliferación del tejido fibroso intersticial, según la describieron los primeros autores. Las discrepancias de opinión proceden de haberse recalcado otros puntos, algunos de los cuales quizás no formen parte de la dolencia en sí misma.

Preséntanse 3 historias clínicas. En un caso, la duración desde la iniciación de los síntomas hasta la muerte fué de quince años, representando el período más largo comunicado. Otro enfermo fué tratado con córticosteroides, constituyendo el vigésimo caso tratado en esa forma que se haya descrito. Lo mismo que en la mayoría de los tratados en forma semejante, la terapéutica fué de poca duración (tres semanas y media) y es difícil justipreciarla. En el mismo caso, había acentuada hiperplasia muscular, representando esto una de las pocas ocasiones en que se describiera tanta acentuación de la proliferación del músculo liso.

No se ha establecido el puesto que le corresponde a la córticosteroidoterapia, pero se halla poderosamente indicada su iniciación inmediata si se hace el diagnóstico en la incipiencia. De 4 de los enfermos, 3 están todavia vivos, representando una sobrevivencia de 75 por ciento en este grupo, mientras que sólo viven 3 por ciento de todos los demás casos descritos.

Resume

Sclérose pulmonaire interstitielle diffuse (syndrome de Hamman-Rich). Rapport sur trois cas

Le nombre des cas de sclérose pulmonaire interstitielle diffuse (syndrome de Hamman-Rich) rapportés comprend moins de 65 cas. Tous les cas rapportés présentent les caractères fondamentaux ordinaires d'une prolifération de tissus fibreux, comme il a été décrit par les auteurs originaux. Il y a divergence d'opinion quant à l'importance de certaines autres caractéristiques, dont quelques unes pourraient n'être pas spécifiques.

Trois observations de malades sont rapportées. Dans un cas, la durée depuis le début des symptômes jusqu'à la mort a été de quinze ans, ce qui représente la durée la plus longue rapportée jusqu'à présent. Un autre malade a été traité par les corticostéroïdes, c'est le vingtième cas ainsi traité. De même que dans la plupart des autres cas traités de façon similaire, la thérapeutique a été de courte durée (trois semaines et demie) et il est difficile de l'évaluer. Dans ce même cas il existait une hyperplasie musculaire prononcée, ce qui représente un des rares cas où la prolifération du muscle lisse ayant été rapportée a été aussi importante.

La place de la corticostéroïdo-thérapie n'a pas encore été établie, mais il y a lieu de l'instaurer d'urgence si le diagnostic est porté précocement. Trois des quatre malades sont encore vivants, ce qui représence pour le groupe un taux de survie de 75%, alors que dans tous les autres cas rapportés la survie n'est que de 3%.

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THE ROLE OF PNEUMOPERITONEUM IN THE NONSURGICAL TREATMENT OF ESOPHAGEAL HIATAL HERNIA[1]

BERNARD MAISEL

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Introduction

During the past six years, the writer has studied the value of pneumoperitoneum in the management of selected and complicated problems of esophageal hiatal hernia in elderly patients (1–4). Pneumoperitoneum, the injection of air into the abdominal cavity, has proved a useful form of treatment for patients with the signs and symptoms of esophageal hiatal hernia.

A major concern today is how best to treat an esophageal hiatal hernia in a geriatric patient when a careful course of medical therapy has failed to control the symptoms and complications of the hernia, and surgical repair cannot safely be undertaken. It is the writer's practice to recommend surgical repair of symptomatic hiatal hernias when these are not amenable to a medical regimen (1).

Two years ago, a patient was admitted to the hospital who presented a most complicated problem. She had angina, severe weight loss, severe upper gastrointestinal dysphagia, gastrointestinal bleeding attributable only to the esophageal hiatal hernia, a paralyzed right diaphragm with paradoxical motion, and a markedly contracted pulmonary ventilatory function as a result of severe asthma. Since this woman was not responsive to her medical supportive regimen, and since hiatal herniaplasty could hardly be considered, she has been treated during the past two years with pneumoperitoneum. This report presents the rather startling clinical improvement and benefit which ensued as a result of this new treatment.

Case Report

The patient, Mrs. B., a 61-year-old woman, was referred to the New York Hospital—Cornell Medical Center in May, 1956, because of severe asthma and a severe gastrointestinal upset.

This patient was in excellent health until five years prior to admission. At that time, she developed attacks of gaseous eructation, right upper quadrant crampy pain that was referred to the right infrascapular area. A cholecystogram revealed many stones in the gall bladder. She was told that she had an esophageal hiatal hernia. A cholecystectomy was done and, following this, the patient was relieved of her symptoms. Her family physician suggested that she follow a six-feeding gastric soft diet, which he outlined.

Two and a half years prior to admission, the patient noticed the onset of exertional dyspnea that steadily became worse until she suffered with four- to five-step dyspnea on flat walking, and two-step dyspnea on climbing stairs. She simultaneously developed a pressing sharp substernal pain that radiated from the precordial area through to the intrascapular area. An electrocardiogram was normal. A gastrointestinal barium study revealed a large hiatal hernia with a gastric ulcer in the herniated segment of stomach. The patient was treated with antacids, barbiturates, vagal blocking agents, a strictly enforced six-feeding

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gastric soft diet, nitroglycerin, and pentaerythritol tetranitrate (Peritrate®). During the succeeding year, the marked dyspnea became less bothersome, but the oppressive substernal pain persisted.

One year prior to admission, the patient's case was again completely evaluated because of a marked increase in the degree of her dyspnea and an exceedingly bothersome and almost persistent substernal pain that was called "angina." A gastrointestinal series revealed a large hiatal hernia without evidence of ulcer. An electrocardiogram was within normal limits. No pulmonary function studies were done.

Five months prior to admission, the patient's dyspnea became crippling, and she was no longer able to carry on her household chores. She raised a half cupful of yellow, thick sputum each day. The attacks of dyspnea became a matter of family and patient crises, and at times lasted most of a day. These attacks were relieved by intramuscular administration of epinephrine and intravenous aminophyllin. The patient was maintained on antihistamines and a variety of nebulized bronchodilators. She rapidly lost a great deal of weight, suffered with precordial pain, and began to suffer with gaseous eructation and fatty food intolerance. She was thought to have a post-cholecystectomy syndrome, as well as angina and the symptoms of an esophageal hiatal hernia.

The patient had always been quite well prior to the present illness except for mild "sinus trouble." A tonsillectomy had been performed at the age of forty. She had never noticed bloody or tarry stools. She smoked no cigarettes, and denied any allergies.

At the time of admission, Mrs. B. was a well-developed, thin, markedly dyspneic white woman in obvious distress, even though propped up in bed. She held on to the mattress, raising her accessory muscles with respirations that were accompanied with an audible wheeze with each inspiration and a louder gurgling sound with each expiration. The blood pressure was 148 systolic and 74 diastolic in mm. of mercury and the temperature was 37.3°C. No postnasal drip was noted, and the sinuses were not tender to palpation. The trachea was in the midline. The chest was emphysematous in type. The heart was not enlarged to percussion, the sounds were of good quality, and no murmurs were audible. However, it was difficult to hear the heart sounds easily because of the overwhelming wheeze in both lung fields. The chest was hyper-resonant to percussion. An inspiratory and expiratory wheeze was audible over both lung fields anteriorly and posteriorly. The abdomen was soft, and no masses were felt. There were well-healed cholecystectomy and appendectomy scars without apparent hernia.

The admission urine was normal, the hemoglobin was 11.5 gm. per 100 ml.; the erythrocyte count was 6,000 per cu. mm.; the leukocyte count was 10.3. The differential count revealed 27 per cent lymphocytes, 11 per cent monocytes, 20 per cent eosinophils, 42 per cent polymorphonuclears. The hematocrit was 38; the sedimentation rate 41: a serologic test for syphilis (Mazzini) was negative. The sputum was repeatedly negative for tubercle bacilli and showed only the normal nose and throat flora. The stools were repeatedly guiac-positive in five examinations, varying trace to 3-plus. The admission electrocardiogram revealed a normal pattern, as did all subsequent electrocardiograms. The chest roentgenogram revealed a high right diaphragm. The mediastinal and cardiovascular silhouettes were at the upper limit of normal. The bronchovascular markings were prominent. A barium study of the upper gastrointestinal tract revealed (figure 1) a large combined "sliding" and "para-esophageal" hiatal hernia with approximately four-fifths of the proximal end of the stomach extending above the diaphragm. The distal portion of the stomach and duodenum were dependent. The duodenal bulb was normal. No ulcer was seen, and there was no obstruction. The right diaphragm was high, paralyzed, and had a paradoxical motion with phases of respirations. The vital capacity was 1,583 cc., which was 53 per cent of the normal predicted value. The administration of Vaponefrin® did not appreciably change this, for it was 1,794 cc., or 57 per cent of the predicted normal, after the use of Vaponefrin. The maximal breathing capacity was 25 liters per minute, or 38 per cent of the predicted normal. After administration of Vaponefrin, it was 28 liters per minute, or 43 per cent of the predicted normal. The values suggested a marked reduction of vital capacity and of maximal breathing capacity, and these suggested the presence of a con-

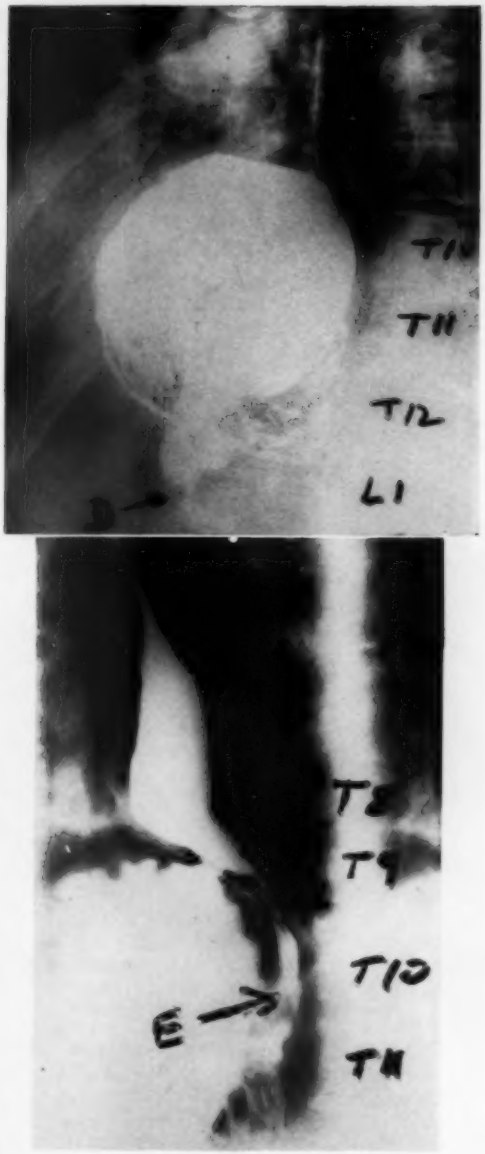

FIG. 1. The barium study of the esophagus and stomach prior to pneumoperitoneum revealed a large combined type of sliding and para-esophageal hiatal hernia. Most of the stomach is found in the hernia sack lying behind the heart and extending as high as thoracic vertebra 9. The esophageal-gastric junction (*E*) lies at the level of thoracic vertebra 10. The pyloric canal (*D*) is found at the level of lumbar vertebra 1, almost at the diaphragmatic hiatus.

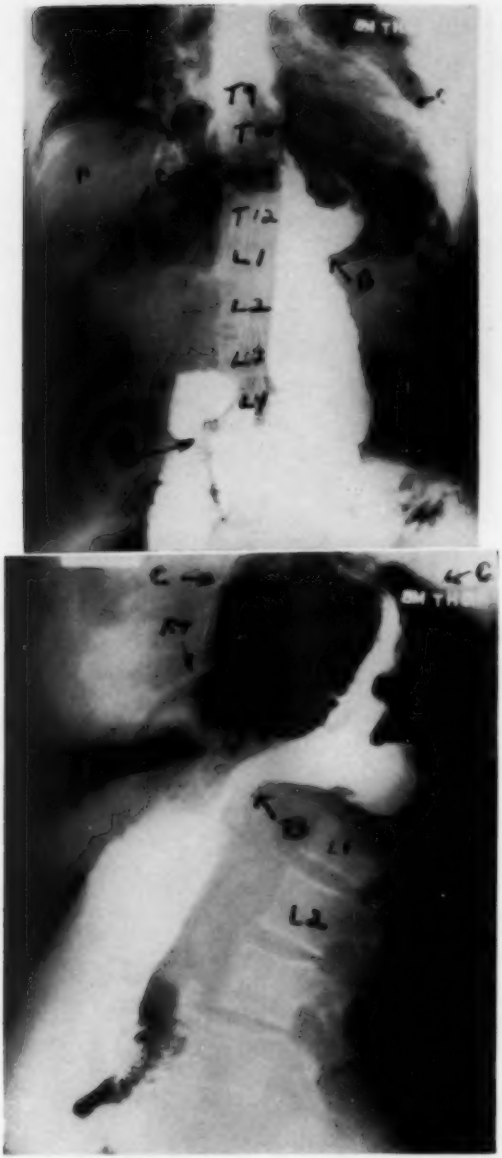

FIG. 2. The barium study of the esophagus and stomach after pneumoperitoneum demonstrated air filling the huge hernia sack (*C*). Almost all of the stomach has been reduced out of the mediastinum and returned to the peritoneal cavity. A small segment of gastric cardia is noted above the diaphragm. This segment intermittently dropped into the peritoneal cavity when seen on fluoroscopy. The redundant esophagus straightened at this time. The tightening and sphincteric effect of the elevated diaphragm is noted at *B*. The pyloric canal (*D*) is found below lumbar vertebra 4.

strictive bronchiolar problem with appreciable limited pulmonary function. The paralyzed right diaphragm and the presence of the large esophageal hiatal hernia were believed to be further anatomic bases for the marked reduction in vital capacity. The skull air sinus roentgenograms showed a chronic pansinusitis. Extensive cutaneous allergy tests revealed only mild sensitivity to mold and house dust.

The clinical formulation of this case was obviously exceedingly difficult. The patient was treated with bronchodilators and chemotherapy, and oxygen was frequently administered by mask. The gastrointestinal signs and symptoms were treated with antacids, elevation of the head of the bed, a six-feeding gastric soft diet, and sedatives. Because she continued to complain of gaseous eructation, fatty food intolerance, and substernal pain, surgical consultation was sought with the hope that this large hiatal hernia might be repaired. Because of her marked loss of ventilatory function, and because of the presence of a paralyzed right diaphragm, all who saw her in surgical consultation believed that surgical repair was impossible. She was therefore referred for possible pneumoperitoneum therapy. She was considered to be an exceedingly "poor-risk" patient, who might very well not respond to such therapy.

The pneumoperitoneum was initiated on May 31, 1956, with the introduction of 800 cc. of air. Fluoroscopy and roentgenography (figure 2) following this revealed a small pneumoperitoneum beneath both diaphragms and air filling the hernia sack. The patient responded rapidly to this treatment, and within five weeks was discharged. She has been followed in the Pneumoperitoneum Hiatus Hernia Clinic, and has continued to maintain complete relief from her gastrointestinal signs and symptoms and from her anginal symptoms.

The management of the patient's asthma has not proved to be as difficult a problem as it was prior to the use of pneumoperitoneum. Intermittently, during the past year and a half of pneumoperitoneum therapy, she has had asthmatic attacks that responded to the administration of intramuscular and nebulized epinephrine. This improvement was sufficient to constitute an unexpected therapeutic dividend. Because of the improvement in the clinical course of the patient's asthma, the cardiopulmonary functions were repeated on December 6, 1956.

The vital capacity was 1,483 cc., or 47 per cent of the predicted normal, and after the administration of Vaponefrin was 1,708 cc., or 54 per cent of the predicted normal. The maximal breathing capacity was 30 liters per minute, or 46 per cent of the predicted normal; after the administration of Vaponefrin, the maximal breathing capacity was 39 liters per minute, or 58 per cent of the predicted normal. It was believed that the over-all pattern of pulmonary function was similar to that noted prior to the administration of pneumoperitoneum. The maximal breathing capacity was slightly greater than it was prior to the administration of pneumoperitoneum, and increased more effectively following the use of nebulized Vaponefrin.

In view of the fact that the patient had been treated with a good course of chemotherapy and antimicrobials, it was thought that it would be difficult to ascribe the improvement in her ventilatory function to the pneumoperitoneum.

On December 5, 1957, following a five-day attack of Asiatic influenza, the patient's family doctor hospitalized her at the community hospital because of a

complicating pneumonia. She was treated with oxygen, antimicrobials, and bronchodilators, and made a rather dramatic recovery. Because of this pulmonary disease, it was not considered suitable to resume the pneumoperitoneum therapy during January or February, 1958. It has been rather surprising that the patient has continued to do well and has no precordial pain or gastrointestinal complaints, and it is the present plan to resume pneumoperitoneum therapy only when necessary.

Discussion

A severely ill woman presented the problem of an hiatal hernia that had produced an anginal syndrome, a post-cholecystectomy syndrome, weight loss, and gastrointestinal bleeding. A number of different physicians in her community attempted to control these signs and symptoms and to treat her severe asthma and dyspnea. Although carefully administered, each of the medical regimens failed to effectively control these complications. A rigidly enforced and carefully organized medical program established at this hospital failed to control the symptoms and signs of the esophageal hiatal hernia and asthma. Surgical repair of the hiatal hernia was carefully considered. All who saw her believed that the complicating asthma, paralyzed right diaphragm, and markedly contracted ventilatory function made her a grave operative risk for either a transthoracic or a transabdominal hiatal herniaplasty.

Under these circumstances, pneumoperitoneum therapy was resorted to for the management of the symptoms of hiatal hernia. This treatment, administered on an ambulatory basis during the past year and a half, effectively controlled the hernia. The patient is now able to do all of her family chores and to resume her normal social functions. The pneumoperitoneum therapy did not aggravate her asthma, but rather seemed to make it less difficult to control the symptoms of asthma and the markedly contracted ventilatory function.

The anatomic and physiologic effects of pneumoperitoneum have been studied experimentally, and the clinical application to gastric and splenic surgery has been reported (5–8). Pneumoperitoneum produces a striking visceroptosis of the stomach and an elevation of the diaphragm. It is difficult to explain the exact mechanism by which pneumoperitoneum abolishes the symptoms and signs of hiatal hernia. It is not possible to say that the herniated segment of gastric cardia was dropped out of the mediastinum, and that this explains the relief noted. This does not occur in each patient treated with pneumoperitoneum (3). Certainly, when the herniated segment is reduced, diaphragmatic irritation produced by the gastric cardia is abolished and, in these cases, this is a plausible explanation of the relief. It is the logical mechanism of relief noted in this case.

Another effect of pneumoperitoneum is the elevation of the diaphragm. As the diaphragm is stretched and elevated, it produces a tightening at the esophageal crus (figure 3). It has been found that this tightening of the diaphragm about the lower esophagus will produce a sphincter-like effect, slowing barium as it is swallowed and preventing the rumination of gastric contents (3). It is possible that the control of rumination of gastric juices into the esophagus by the dia-

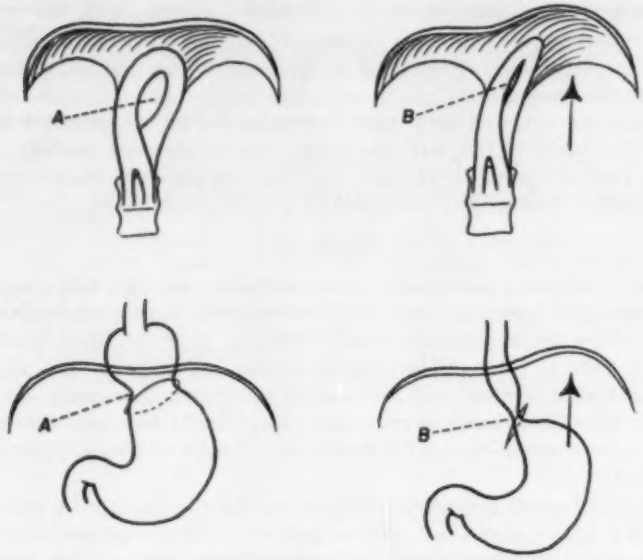

FIG. 3. Pneumoperitoneum may be shown diagrammatically to produce visceroptosis of the stomach from the mediastinum and elevation of the diaphragm. As the diaphragm is elevated, the musculature about the esophageal hiatus is tightened, so that the large aperture *A* becomes the small aperture *B*. This tightening of the diaphragm about the lower end of the esophagus will produce a sphincter-like slowing of barium as it is swallowed, and, more importantly, will prevent the reflux of gastric contents into the esophagus.

phragmatic sphincter produced by pneumoperitoneum allows superficial mucosal ulcers in the gastric cardia and lower esophagus to heal, and thus abolishes the symptoms. Healing of the superficial ulcers will stop the gastrointestinal hemorrhage that may, as in this case, accompany an esophageal hiatal hernia.

Inasmuch as the signs and symptoms related to esophageal hiatal hernia are aggravated at night when the patient is lying flat in bed, it is recommended that the head of the bed be elevated eight inches on "shock blocks." This position for sleep maintains the visceroptotic effect and prevents rumination of gastric juices, for these juices would have to run up-hill against gravity.

Anyone employing this therapeutic procedure would be especially interested in the safety of the procedure. The writer has employed this therapeutic measure, with no fatality, during the past decade for the treatment of pulmonary tuberculosis and hiatal hernia. Many patients (as did the present patient) complain of moderate sticking pain at the posterior apex of each shoulder. This pain is easily controlled with small doses of narcotics, and disappears after several days. Phrenic nerve stimulation is believed to be the root pathway of the pain.

Those who might wish to employ this procedure would also be interested in the possible effects of pneumoperitoneum on ventilatory function in emphysema-

tous patients. No deleterious effects have been encountered by the writer; in fact, since pneumoperitoneum can be expected to reduce the residual air capacity of the lungs, ventilatory efficiency of respiration may be enhanced, as seemed to be true in the present case.

It is recommended that the patient be hospitalized for the initial pneumoperitoneum treatment. In this way, the patient can be observed carefully, and his shoulder pain can be safely relieved. The follow-up pneumoperitoneum therapy can be safely and effectively continued on an ambulatory basis.

Summary

Pneumoperitoneum proved effective in controlling the signs and symptoms of esophageal hiatal hernia in a seriously ill 61-year-old woman who suffered with angina, severe upper gastrointestinal dysphagia, gastrointestinal bleeding attributable only to the esophageal hiatal hernia, a paralyzed right diaphragm with paradoxical motion, and a markedly contracted pulmonary ventilatory function. The classic medical treatment proved ineffective, and she was considered a grave operative risk for either transthoracic or transabdominal hiatal herniaplasty.

Pneumoperitoneum was administered on an ambulatory basis for more than a year and a half, and did not produce any clinically recognizable interference with the patient's badly damaged cardiopulmonary function. In fact, her ventilatory function was improved during the course of the pneumoperitoneum therapy.

Sumario

El Papel del Neumoperitoneo en el Tratamiento Incruento de la Hernia del Hiato Esofágico: Presentación de un Caso

El neumoperitoneo se mostró eficaz para dominar los signos y síntomas de una hernia del hiato esofágico en una enferma de gravedad que tenía 61 años y padecía de angina, seria disfagia de la porción superior del tubo gastrointestinal, hemorragia gastrointestinal imputable únicamente a la hernia del hiato esofágico, parálisis del lado derecho del diafragma con movimiento paradójico y destacada contracción de la función ventiladora del pulmón. El tratamiento médico clásico resultó ineficaz y se consideró a la enferma como grave riesgo operatorio para la hernioplastia hiatal ya transtorácica o transabdominal.

Se aplicó el neumoperitoneo a base ambulante durante más de año y medio sin producir la menor obstaculización clínicamente reconocible de la muy afectada función cardiopulmonar de la enferma. Es más, la función ventiladora mejoró durante la neumoperitoneoterapia.

Resume

Le rôle du pneumopéritoine dans le traitement non chirurgical de la hernie oesophagienne hiatale: Rapport sur un cas

Le pneumopéritoine s'est montré efficace pour contrôler les symptômes de la hernie oesophagienne hiatale chez une femme de 61 ans dont l'état était grave. Cette malade avait une angine de poitrine, une importante dysphagie gastro-intestinale, des hémorragies intestinales uniquement dues à la hernie oesophagienne hiatale, une paralysie du diaphragme droit avec mouvement antinomique et une fonction de ventilation pulmonaire nettement limitée. Le traitement médical classique s'était montré inefficace et on considérait ce

cas comme un risque opératoire grave, soit pour la hernioplastie hiatale thoracique ou transabdominale.

Le pneumopéritoine a été administré de façon ambulatoire pendant plus d'an an et demi sans altération cliniquement apparente de la fonction cardio-pulmonaire déjà très endommagée de cette malade. En fait, la fonction ambulatoire s'est améliorée au cours du traitement par le pneumopéritoine.

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BRONCHIOLAR (ALVEOLAR CELL) CARCINOMA[1]

Failure to Cause Symptoms for More Than Twelve Years

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Introduction

On the basis of retrospective observation of chest roentgenograms, made fortuitously in cases in which, subsequently, carcinoma of the lung was proved histologically, Rigler (1) came to the conclusion that this tumor grows more slowly and over a longer period of time than has been generally supposed. He stated that many cases of carcinoma of the lung arise peripherally, remain isolated and symptomless for long periods of time, but eventually grow centrally and invade a major bronchus, with development of symptoms at that time. He estimated that the average time between the first roentgenographic appearance and the development of symptoms may well exceed two years. One of the cases which he published was of a bronchiolar carcinoma in a 60-year-old woman who was practically asymptomatic for more than six years. Previously, a case (2) in a 16-year-old boy who remained asymptomatic for three years, and another (3) in a 72-year-old woman who remained without symptoms for four years, were reported.

Recently, a case of bronchiolar carcinoma was encountered at the Veterans Administration Regional Office, Roanoke, Virginia; the patient was asymptomatic for a longer period of time than the patient of any other case published so far.

Case Report

A 53-year-old white male was first admitted to the Veterans Administration Hospital, Richmond, Virginia, on December 6, 1954, for treatment of a right hydrocele. This was resected and the patient was discharged on December 13, 1954. A routine chest roentgenogram revealed a mass 3 cm. in diameter at the periphery of the third anterior intercostal space on the right, which, on lateral exposure, appeared to be located in the anterior segment of the right upper lobe. The patient was readmitted to the hospital for evaluation and treatment of the lung lesion on January 3, 1955.

The patient had had no symptoms since 1945 except minimal cough. This cough had not grown worse. During the year or two prior to his admission, he smoked 10 cigarettes a day, but had been a heavy smoker before that time. Physical examination, including that of the chest, was entirely normal. There were no palpable lymph nodes. Complete blood count, urinalysis, cardiolipin, blood urea nitrogen, glucose, total protein, albumin, globulin, cholesterol, and cephalin-flocculation were within normal limits. A tuberculin reaction to first-strength purified protein derivative (PPD) was negative; to second-strength PPD, it was 2-plus. Blastomycin, coccidioidin, and histoplasmin skin tests were negative. An electrocardiogram was within normal limits. Repeated sputum specimens were negative for *Mycobacterium tuberculosis* and for tumor cells. Bronchoscopy on January 5, 1955, revealed normal findings, and no tumor cells were found in the bronchial washings.

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[1] From the Veterans Administration Regional Office, Roanoke, Virginia.

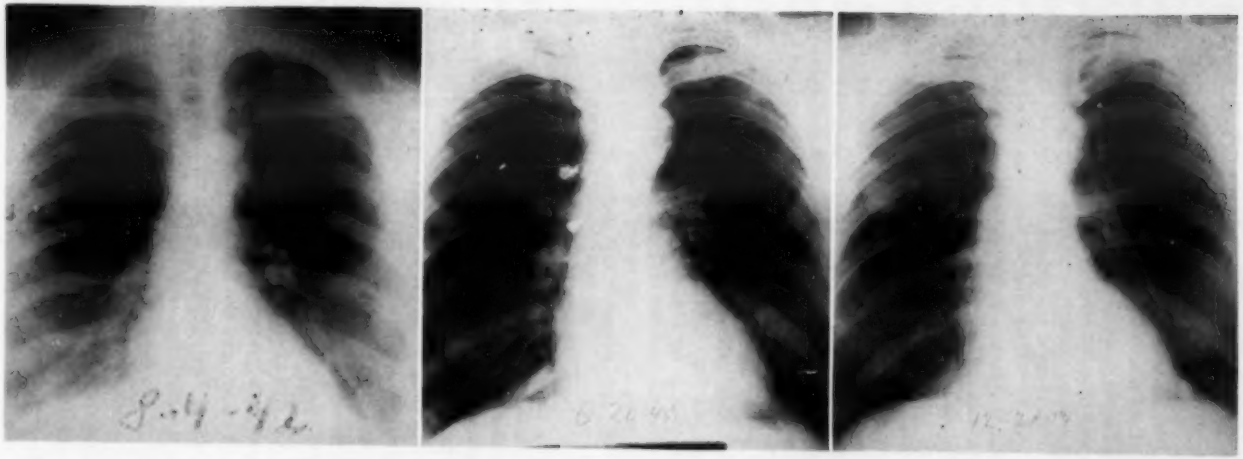

FIG. 1 (Left). Induction film, obtained on August 4, 1942, showing lesion at the periphery of the third anterior intercostal space on the right.
FIG. 2 (Center). "Separation" film, obtained on June 20, 1945. The lesion had not increased in size from the time when the first film (figure 1) was obtained.
FIG. 3 (Right). Roentgenogram obtained on December 28, 1954, showing significant enlargement of the lesion.

A right thoracotomy was performed on January 14, 1955. A 2-by 3-cm. firm mass was found in the anterior segment of the upper lobe, abutting on the minor fissure. This was resected. Frozen-section diagnosis revealed alveolar cell carcinoma. There was no marked mediastinal lymphadenopathy. A few small anthracotic lymph nodes up to 0.5 cm. in diameter were noted in the anterior aspect of the hilus and in the inferior pulmonary ligament. Classic pneumonectomy by individual ligation technique was performed. The lymph nodes just below the inferior pulmonary vein were removed separately.

A biopsy of this specimen showed numerous tannish-white nodules which on section appeared homogeneous and of semi-solid consistency. Microscopic examination showed nodules made up of atypical, poorly defined cells with a moderate amount of eosinophilic granular cytoplasms, enclosing fairly uniform round or oval vesicular nuclei. The cells tended to align themselves as sheets and formed a typical alveolar structure. They secreted a large amount of deeply eosinophilic material which distended the pseudo-alveoli and separated the lobules of the growth. At the periphery of the nodule, the cells occasionally grew along the walls of the adjacent compressed alveoli. They formed numerous papillary projections. Similar cells were also noted in a hilar node.

The postoperative course was uneventful. Bronchoscopy on February 1, 1955, disclosed that the bronchial stump was well healed. The patient was discharged from the hospital on February 4, 1955. Follow-up examinations, first at three-month and, subsequently, at six-month intervals failed to show metastasis in the left lung, and the patient's general condition remained very good. The latest follow-up examination was on December 12, 1957.

When the patient's military service films were reviewed recently for administrative reasons, it was noted that the lesion, although smaller in size, was already present both on the induction film (figure 1), dated August 4, 1942, and the "separation" chest roentgenogram (figure 2), dated June 20, 1945. So far as can be determined by comparison of the 4- by 5-inch induction chest roentgenogram and the 14- by 17-inch "separation" film, there was no increase in the size of the mass during this period of time; but there was significant enlargement between June, 1945, and December, 1954 (figure 3).

Discussion

Beaver and Shapiro (4), by studying 7 cases of their own, came to the conclusion that chronic pulmonary parenchymal inflammation lays the groundwork for the later development of alveolar cell carcinoma, and believed that they would find further confirmation of their view by analyzing 121 of the cases collected previously by Storey (3). While it is theoretically possible that in the present case the roentgenographic shadow at the right midlung field was a granulomatous lesion in 1942 and 1945, and that, subsequently, a malignant tumor developed (within this area or around it), there is nothing to support this assumption. Skin tests for fungi were negative, and so was the tuberculin test with first-strength PPD. Careful microscopic study did not disclose any granulomatous elements incorporated in the tumor itself or in the adjacent tissues. There was no calcification within or around the lesion.

In Storey's series (3), 11 of 154 patients (7 per cent) were entirely asymptomatic, and the duration of symptoms was forty-eight months or more in 12 of 151 cases (8 per cent); in 26 per cent of the patients, the first roentgenographic appearance was that of a solitary peripheral nodule.

A review of the literature reveals contradictory views concerning the relatively benign character of bronchiolar carcinoma. While Overholt and his associates (5) reported that surgical resection of these lesions has a good prognosis, Davis, Peabody, and Katz (6) stated that their results in bronchiolar carcinoma were

the worst ones in the group of malignant solitary nodules. This occurred despite the fact that these were mostly small asymptomatic lesions, unaccompanied by lymph node involvement, which, upon microscopic examination, were better differentiated than the average adenocarcinoma. In contradistinction to the patients who were asymptomatic for a long period of time and despite roentgenographic findings, a case (7) of a 41-year-old woman was reported, whose chest film was entirely normal just a few weeks before her symptoms developed, which consisted of pulling pain in the chest and shortness of breath six weeks before a subsequent film revealed multiple small areas of increased density in both lungs. Some pathologists believe that true bronchiolar carcinoma cases have poor prognosis, and they can and should be differentiated from the relatively benign subgroup of tubular adenomas.

Summary

A number of observations during the past few years indicate that malignant tumors may remain asymptomatic for a formerly unsuspected length of time. This is illustrated by a histologically proved case of bronchiolar carcinoma which presented no symptoms for twelve and one-half years. The fact that a solitary pulmonary peripheral nodule is asymptomatic and shows no change in its size for a long period of time does not militate against its malignant nature.

Summario

Carcinoma Bronquial (Células Alveolares) Asintomático Más de 12 Años

Varias observaciones realizadas durante los últimos años indican que los tumores malignos pueden permanecer asintomáticos durante un período de tiempo que no se sospechaba anteriormente. Así lo demuestra un caso comprobado histológicamente de carcinoma bronquiolar que no produjo síntomas por espacio de doce años y medio. El hecho de que un nódulo pulmonar periférico solitario sea asintomático y no cambie de tamaño durante un período prolongado de tiempo no milita contra su naturaleza cancerosa.

Resume

Carcinome bronchiolaire (cellule alvéolaire) asymptomatique pendant plus de 12 ans

Au cours de ces dernières années, un certain nombre d'observations indiquent que les tumeurs malignes peuvent demeurer asymptomatiques pendant une période de temps que l'on ne pouvait imaginer autrefois. Ceci est illustré par un cas démontré histologiquement où le carcinome bronchiolaire n'a présenté aucun symptôme pendant 12 ans 1/2. Le fait qu'un nodule périphérique pulmonaire unique soit asymptomatique et sans varier de dimensions pendant une longue période de temps n'infirme pas le caractère de malignité de cette tumeur.

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Notes

STUDIES OF THE PAS SALT OF ISONIAZID IN THE TREATMENT OF TUBERCULOSIS

Over the past four years several reports[1-8] have appeared on the tuberculostatic action of isonicotinic hydrazide-*p*-aminosalicylate[9]. (This compound will be referred to hereafter as I-P salt.) The reports that have appeared to date have been favorable. The question arose whether the I-P salt was superior to treatment with isoniazid and PAS. This question was approached by carrying out clinical and laboratory studies on the efficacy of the I-P salt for patients who had failed to respond to treatment with isoniazid, PAS, and streptomycin.

Twenty long-term patients were selected for treatment with the I–P salt. One of these patients is excluded from the study because he underwent thoracic surgery during I–P salt therapy.

Sixteen of the patients had been diagnosed as having far advanced pulmonary tuberculosis; 2, moderately advanced pulmonary tuberculosis; and one, minimal pulmonary tuberculosis following a lobectomy. Of the 19 patients treated with I–P salt, 4 were women with an average age of thirty-four years, the youngest being twenty-three and the oldest forty-two years of age. Fifteen patients were men with an average age of forty-two years, the youngest being thirty and the oldest sixty-one years of age. These 19 patients all had sputum positive for tubercle bacilli on culture prior to treatment. They were patients who had failed to respond to all previous therapy.

Chest roentgenograms, sputum status, and general clinical condition were used to determine what response there had been to previous chemotherapy. The same criteria were used to evaluate the results of the I–P salt study. In addition, the selected cases were patients who could not be considered candidates for any further form of collapse or resection procedures.

The I–P salt was administered for the first five months of the study in a total daily dosage of 600 mg., given orally three times daily in equally divided doses. From the sixth month onward, the daily dosage was increased to 900 mg., and pyridoxine was also given to prevent neuritis.

Monthly roentgenograms were interpreted and changes recorded. Before treatment *M. tuberculosis* was cultured from the sputum of all but one patient. This patient had acid-fast bacilli which were atypical and photochromogenic. After the initiation of treatment, specimens for culture were obtained from all patients at approximately four-week intervals. The concentrated specimens were cultured on Löwenstein-Jensen medium and on Tarshis blood agar.[10] The amount of growth was recorded as "innumerable"—a mass of colonies which cannot be counted; "many"—50 or more colonies on the slant; "scattered"—25 to

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TABLE 1

DATA ON PREVIOUS CHEMOTHERAPY AND I-P SALT THERAPY OF PATIENTS INCLUDED IN CLINICAL STUDY

Name	Sex-Age	Time in Hospital	Previous Chemotherapy							I-P Salt Therapy					
			Time (months)				Cultural Results†			Time (months)			Cultural Results‡		
			SM*	INH	PAS	INH and PAS	Before	During	After	Total	600 Mg.	900 Mg.	Before	During	After
		months													
E. B.	M-42	57	48	34	29	29	M-I	M-I	S-M	7½	5	2½	S-M	M-R-O	O
J. Mc.	M-47	69	40	45	10	—	M§-I	M	M	7½	5	2½	M	M-S-O	O
W. Da.	F-23	45	45	38	8	—	M§-I	M	M-I	7½	5	2½	I	I-M	M
B. B.	M-37	47	47	26	18	8	M	M	S-M	7½	5	2½	S-M	M	M
F. F.	M-50	11	—	11	11	11	—	R	R-F	7½	5	2½	R-F	M-S-F	M
W. Dr.	M-35	149	47	42	16	5	M-I	M	M-I	7½	5	2½	M-I	M	M
H. T.	M-36	83	40	45	24	14	M	I	M-I	7½	5	2½	M-I	M-I	M
M. C.	F-31	49‖	16	17	3	—	I§	M	M	7½	5	2½	M-I	M-I	M
R. M.	M-39	44	41	41	28	23	R-M	M	M-I	6	5	1	M-I	M-I	M
J. Do.	M-39	36	35	26	10	6	R-M	S-M	F-M	7½	5	2½	S-M	M	M
J. Da.	M-37	47	47	36	26	17	F-M	M-I	M-I	7½	5	2½	M-I	M-I	M
R. N.	M-30	97	49	44	16	16	M-I	M	M-I	7½	5	2½	M-I	M-I	M
C. S.	M-32	36	40	45	44	38	S-M	M-I	M-I	7½	5	2½	M-I	M-I	M
J. S.	M-37	92	40	42	16	10	F-I	M-I	M-I	7½	5	2½	M-I	M-I	M
A. B.	M-52	66	36	43	16	10	M-I	M	M-I	7½	5	2½	M-I	M-I	M
E. H.	F-42	68‖	5	14	21	13	M	M	M-I	6	5	1	I	I	I
M. Wa.	M-39	12	7	11	2	2	S	S	M-I	6	5	1	M-I	M-I	M
M. Wi.	F-41	79‖	19	45	41	31	M-S	R-M	M-I	5	5	—	M-I	S-M	—¶
L. T.	M-51	41	33	41	12	11	M-I	M	M	2½	2½	—	M	M	—¶

* The following abbreviations are used: SM—streptomycin; INH—isoniazid; PAS—para-aminosalicylic acid.

† The "before," "during," and "after" periods under cultural results refer to the period of therapy with isoniazid and PAS. In most cases approximate averages of numerous cultures are given. The following abbreviations are used: I—innumerable colonies; M—many (more than 50 colonies); S—scattered (25 to 50 colonies); F—few (10 to 25 colonies); R—rare (less than 10 colonies); O—negative culture.

‡ Cultural results refer to period of I-P salt therapy, except where indicated otherwise.

§ Cultural results refer to period of therapy with streptomycin and isoniazid.

‖ Patient had been hospitalized previously.

¶ Patient died.

50 colonies on a slant; "few"—10 to 25 colonies on a slant; "rare"—up to 10 colonies on a slant.

Drug-susceptibility tests were conducted on Löwenstein-Jensen medium after primary isolation on solid medium (Löwenstein or blood agar). These tests were performed on pretreatment cultures and at approximately four-week intervals throughout the study. All media used in this study were freshly prepared. The concentrations of drugs used were: I–P salt, 50 γ per ml., 5 γ per ml., and 1 γ per ml.; streptomycin, 100 γ per ml., 10 γ per ml., and 0.5 γ per ml; isoniazid, 5 γ per ml., 1.0 γ ml., and 0.2 γ per ml.; PAS, 250 γ per ml., 100 γ per ml., and 10 γ per ml. Each of the susceptibility-test culture tubes was inoculated with one drop of a heavy suspension (approximately the density of a McFarland standard No. 1) of the isolated tubercle bacilli. The selection of the concentrations of I–P salt was based primarily on the work of Brodhage (3), who found in a study of resistance of *M. tuberculosis* to I–P salt that none of the strains he tested were resistant to 50 γ per ml.

The following laboratory examinations were made prior to the administration of I–P salt: complete blood count, hematocrit and sedimentation rate determinations; routine urine analysis for albumin and glucose, as well as microscopic examination for cellular elements. These procedures were repeated at intervals of approximately four weeks throughout the period of I–P salt administration and after the drug had been discontinued.

The salient factors in the histories of the 19 patients who were subjected to experimental I-P salt therapy are detailed in tables 1 and 2. It is apparent from these data that all patients had previously received both isoniazid and PAS. (Most of the patients had received these drugs concurrently.) No significant changes were observed in the cultural results prior to I-P salt therapy, and no improvement in the clinical condition of the patients was observed.

The reaction to PAS had been sufficiently serious to discontinue the drug in 6 cases. All but one of these reactions were gastric disturbances. In one case, isoniazid had to be discontinued. In comparison, the I-P salt was discontinued in 2 cases. However, the dosage of PAS (12 gm. per day) was about thirty times as great as the amount contained in the I-P salt dosage.

In 2 of the 19 patients, tubercle bacilli disappeared from the sputum during therapy with the I-P salt. These 2 patients had received isoniazid and PAS treatment for more than two years prior to the initiation of I-P salt therapy.

Susceptibility tests on the tubercle bacilli isolated from the patients (table 3) indicated that all but 3 of the patient-strains were either resistant or partially resistant to isoniazid, and all but 2 were resistant or partially resistant to the I-P salt. Sixteen of the 19 patients were infected with strains of tubercle bacilli resistant to PAS. Streptomycin-susceptibility tests were also carried out but are not reported because they appear to bear no relation to the I-P salt susceptibilities.

Significant changes in the susceptibility to I-P salt during treatment were observed in only 2 cases (*E. B.* and *J. Mc.*). In both cases, the sputum became negative for tubercle bacilli following the emergence of resistant strains. In the remainder of the cases, the drug susceptibility of the patient-strains remained essentially unchanged on repeated susceptibility tests.

Tests for susceptibility to the I-P salt were also carried out in liquid medium, using filtered solutions of the I-P salt. The object was to determine if the high degree of resistance to the I-P salt was the result of its breakdown. All strains were resistant to the I-P salt in the liquid medium. The routine urine and hematologic examinations revealed no pathologic changes which could be attributed to the medication.

All of the reports on clinical trials of the I-P salt in tuberculous infections that have appeared to date have been favorable.[1, 4-8, 10] However, most of the reports shed little

light on the relationship between the efficacy of the I-P salt and that of the multiple-drug regimen of isoniazid-PAS.

The object of the present study was to compare both the bacteriologic and clinical responses to I-P salt therapy with the responses to isoniazid-PAS therapy. The approach was to treat patients with pulmonary tuberculosis who had failed to respond to isoniazid-PAS with the I-P salt. A similar approach was used by Clegg in England. Fourteen of

TABLE 2

SUMMARY OF CLINICAL DATA DURING PREVIOUS CHEMOTHERAPY AND I–P SALT THERAPY

Patient	Status Under Previous Chemotherapy			Status Under I-P Salt Regimen		
	Roentgenogram	Clinical*	Drug Reactions†	Roentgenogram	Clinical	Drug Reactions
E. B.	Cavity left	P-2‡, no change	None	No change	Noninfectious sputum sixth month	None
J. Mc.	Cavity left	P-2, no change	None	No change	Noninfectious sputum fifth month	None
W. Da.	Bilateral cavities	P-3, worse	PAS discontinued; gastric complaints	No change	No change	None
B. B.	Bronchial stump abscess, left	P-1, no change	PAS discontinued; gastric complaints	No change	No change	None
F. F.	Cavity left upper	P-3, no change	None	No change	No change	None
W. Dr.	Bilateral cavities	P-3, worse	PAS and isoniazid discontinued; gastric complaints	No change	No change	None
H. T.	Bilateral cavities	P-3, no change	PAS discontinued; purpura of legs	No change	No change	None
M. C.	Bilateral cavities	P-3, worse	PAS gastrointestinal complaints in 1952; none in 1956	No change	No change	None
R. M.	Bilateral cavities	P-3, no change	Isoniazid reduced; numbness of fingers	No change	No change	I–P salt refused in sixth month (?)

TABLE 2—*Continued*

Patient	Status Under Previous Chemotherapy			Status Under I-P Salt Regimen		
	Roentgenogram	Clinical*	Drug Reactions†	Roentgenogram	Clinical	Drug Reactions
J. Do.	Cavity right upper	P-3, worse atypical acid fast	None	Worse	No change	None
J. Da.	Bilateral cavities	P-3, worse	None	Worse	No change	None
R. N.	Bilateral cavities	P-3, no change	PAS discontinued; gastric complaints	Worse	No change	None
C. S.	Left and midfield cavities	P-3, worse	None	Worse	No change	None
J. S.	Bilateral cavities	P-3, no change	None	Worse	Worse	None
A. B.	Bilateral cavities	P-3, no change	None	Worse	Worse	None
E. H.	Bilateral cavities	P-3, no change	None	Worse	Worse	I–P salt discontinued in 6 months; gastric complaints
M. Wa.	Cavity right upper	P-3, worse	None	Worse	Worse	None
M. Wi.	Bilateral cavities	P-3, worse	PAS discontinued	Worse	Died in fifth month	None
L. T.	Bilateral cavities	P-3, worse	Isoniazid reduced; gastric intolerance	Worse	Died in third month	None

* "Clinical" under previous chemotherapy refers to the year before I–P salt therapy was initiated.

† "Drug reactions" under previous chemotherapy includes only reactions to isoniazid and PAS.

‡ Status of disease according to National Tuberculosis Association classification:
P-1: minimal pulmonary tuberculosis
P-2: moderately advanced pulmonary tuberculosis
P-3: far advanced pulmonary tuberculosis

TABLE 3

SUSCEPTIBILITY TEST ON TUBERCLE BACILLI

Patient	Observations			Interpretation I-P Salt
	PAS	Isoniazid	I-P Salt	
E. B.*	R‡—10	R—5	R—5	PR
†	R—10	R—5	R—50	R
J. Mc.	PR—100	R—5	R—5	PR
†	R—100	R—5	R—50	R
W. Da.	PR—10	R—1	R—1	PR
B. B.	R—250	R—5	R—50	R
F. F.	R—250	R—5	R—50	R
W. Dr.	R 250	R—5	R—50	R
H. T.	R—250	R—5	R—50	R
M. C.	PR—100	R—5	PR—50	R
R. M.	PR—250	R—5	R—50	R
J. Do.	R—250	R—0.2	R—1	PR
J. Da.	R—250	R—5	R—50	R
R. N.	PR—250	R—5	R—5	PR
C. S.	PR—250	R—5	R—50	R
J. S.	PR—250	R—0.2	PR—1	S
A. B.	PR—250	R—5	R—50	R
E. H.	R—250	R—0.2	R—1	PR
M. Wa.	PR—10	R—5	PR—0.2	S
M. Wi.	R—250	R—5	PR—50	R
L. T.	PR—100	R—5	PR—50	R

* Susceptibility tests are pre I-P salt unless otherwise indicated.

† Susceptibility tests on last positive cultures; these are the only strains that underwent changes in susceptibility.

‡ R—resistant; PR—partly resistant; S—susceptible.

the patients reported by Clegg had failed to respond to isoniazid-PAS and, among these, 4 experienced reversal of infectiousness during I-P salt therapy. In the present study, the sputum became negative for tubercle bacilli in 2 of the 19 patients during a 2.5-to 7.5-month trial period. These data suggest that a small proportion of the patients who failed to respond to isoniazid-PAS can be rendered noninfectious by treatment with the I-P salt.

However, some reservations must be attached to such a conclusion. The number of comparisons between multiple-drug isoniazid-PAS treatment and I-P salt treatment that have been reported is too small to make a definitive conclusion possible. Further studies of this type are indicated. Moreover, it is possible that the tuberculous cavities underwent changes during treatment with other chemotherapeutic agents which made them less refractory to I-P salt chemotherapy, although it seems improbable that this should occur in 11 to 28 per cent of the cases. It would be necessary to study the effect of standard isoniazid-PAS treatment on patients who have failed to respond to the I-P salt in order to prove the superiority of the latter.

The clinical condition of 6 of the patients deteriorated during treatment with the I-P salt. Considering the condition of the patients before I-P salt therapy was instituted, it seems unlikely that they would have done better with other forms of chemotherapy.

A comparison between the susceptibility-test data of the strains of tubercle bacilli

isolated before I-P salt treatment and the eventual disappearance of tubercle bacilli from the sputum suggests that susceptibility tests might be of some value in prognosticating treatment responses. Eight of the 19 patients were infected with strains that were "partially resistant" or susceptible to the I-P salt, and the remaining 11 patients were infected with strains that were resistant. The 2 instances of reversal of infectiousness occurred among the "partially resistant" cases.

In summary: A clinical trial of I-P salt (the isoniazid salt of PAS) was carried out on a group of 19 patients with pulmonary tuberculosis. All of the tuberculous infections were of long standing. The patients' disease had failed to respond to streptomycin, isoniazid, and PAS, as well as to other chemotherapeutic agents. Tubercle bacilli were readily isolated from the sputum of all 19 patients before treatment. The therapy with the I-P salt was carried on for two and a half to seven and a half months.

Reversal of infectiousness occurred in 2 patients during the I-P salt treatment. The sputum of these patients has remained negative for tubercle bacilli for seventeen months since cessation of I-P salt therapy. Seven of the remaining 17 patients showed no appreciable roentgenographic change and 10 showed worsening of the disease by roentgenography. Two patients died during the actual course of therapy.

The number of untoward reactions to the I-P salt is considerably smaller than the number of reactions to PAS alone. This appears to be associated with the relatively small amount of PAS contained in the I-P salt.

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October 4, 1957

INVESTIGATIONS INTO THE ROLE OF FUNGI IN PULMONARY DISEASES IN INDIA

For many years mycotic infections of the lung have been regarded as exotic diseases, which were of interest to the specialist but did not concern the average general practitioner or the young medical officer. However, during the last few years evidence has been forthcoming for a change of this point of view. It is now known that mycotic infections occur with sufficient frequency to justify their being considered in the differential diagnosis of all cases of pulmonary diseases in which the etiology is not clear.

It is interesting to note that, while infections due to other fungi have been reported from India, no confirmed case of pulmonary infection by any dimorphic fungi has as yet been reported. Very few reports of cases of pulmonary mycoses have been made in India, and in these cases also the diagnosis was not confirmed by cultural examination. Complete bacteriologic and mycologic investigations were therefore undertaken to find out the true role of fungi in pulmonary diseases.

The present paper is based on investigations carried out in 1956 on sputum from 125 cases of pulmonary diseases from various hospitals and sanatoriums in Rajasthan. Most of the patients had some sort of chemotherapy. They had signs, symptoms, and roentgenographic findings resembling those of pulmonary tuberculosis, but their sputum was persistently negative for acid-fast bacilli on microscopic examination of concentrated specimens. Culture of the sputum was not done at that stage. Tuberculin testing of the patients was also not done.

All sputum specimens were processed as soon as they were received and were subjected to the following tests: As soon as the specimen was received, it was examined microscopically. It was then inoculated on several media for fungi. The sputum was then concentrated and cultured on Löwenstein-Jensen medium, and microscopic examination of the deposit was carried out for acid-fast organisms and fungi.

Microscopic examination of the sputum: the sputum was examined by placing a loopful on a microscopic slide and covering the preparation with a cover glass. If the sputum was tenacious or highly purulent, it was mixed on a slide with a drop of 10 per cent solution of potassium hydroxide for clearing and examined under a cover glass after gently heating over a low flame of the Bunsen burner. Microscopic examination was made with the low and high dry objectives of the microscope. Reduced light was employed because, if the specimens are examined with a bright beam of light, lack of contrast causes the fungal bodies to blend with the background and then it becomes difficult to differentiate them from the cellular material. The tissue phase of many of the fungi found in the sputum is distinctive enough to allow a provisional diagnosis. Although most fungi causing pulmonary infections may be detected in fresh preparations of sputum, some fungi are more easily detected in stained smears, particularly Actinomyces, Nocardia, the Candida, and *Histoplasma capsulatum*. Sputum smears were stained by Gram's method. Sputum was then cultured for fungi, and after culturing it was concentrated by the following methods.

Equal quantities of sputum and 4 per cent sodium hydroxide were mixed in sterile centrifuge tubes, shaken, and put in the incubator. They were left in the incubator for half an hour, being shaken two or three times meanwhile. At the end of about thirty to forty minutes, the supernatant was thrown away. The deposit was resuspended in a small quantity of sterile saline and neutralized with normal hydrochloric acid, using phenolphthalein as an indicator.

Cultures were then made from the deposit on Löwenstein-Jensen's medium. Smears were made from the concentrated deposit and stained by the: Gram method; Ziehl-Neelsen method; and modified Ziehl-Neelsen, using 3 per cent hydrochloric acid in ethyl-alcohol as a decolorizing agent and decolorizing quickly for twenty-five seconds only, as *Nocardia asteroides* is weakly acid fast.

Culture: The sputum was directly inoculated heavily on the following media for the isolation of fungi:

Sabouraud dextrose agar
Sabouraud dextrose agar with 20 units of penicillin and 40 units of streptomycin
Brain-heart infusion glucose liquid medium
Brain-heart infusion agar
Brain-heart infusion agar with 20 units of penicillin and 40 units of streptomycin.
Thioglycollate liquid medium.

The concentrated material was cultured on two tubes of Löwenstein-Jensen medium for the isolation of tubercle bacilli.

For the last 52 cases, actidione was available through the kindness of Dr. Norman F. Conant, and this was incorporated in the medium with penicillin and streptomycin in the proportion of 0.5 mg. per ml. of the medium. Actidione is a very effective cyclohexamide which prevents the growth of fungal contaminants but allows the growth of the pathogens. However the organism *Cryptococcus neoformans* is very susceptible to this fungicide, and for this reason actidione was not added to all of the cultures.

Two sets of each of the Sabouraud and brain-heart infusion agar were used, one with streptomycin and penicillin and the other without penicillin and streptomycin, because the actinomycetes are susceptible to both penicillin and streptomycin.[1] Furthermore, since the aerobic Nocardia and the anaerobic *Actinomyces bovis* can not be distinguished by the appearance of granules and Gram-stained smears, the material collected from the patient was cultured both anaerobically on brain-heart glucose infusion liquid medium and thioglycollate liquid medium and aerobically on the other four media. Cultures suspected of Actinomyces were cultured on glucose-agar medium also.

Two tubes of each medium were inoculated; one set was incubated at room temperature, the other at 37°C.

All cultures composed of yeastlike cells were streaked on corn meal-agar plates for the production of chlamydospores.

Brain-heart infusion containing 3 per cent of the respective sugars was used for the differentiation of Candida isolated from the sputum.

In view of the above and since, in the present investigations, culture and not the biopsy examination was to be the most important procedure and other staining methods (the Gram and the Ziehl-Neelsen) were found equally useful and informative, the periodic acid-Schiff method of staining was not employed. In fact, the periodic acid-Schiff method of staining is essentially useful in the study of tissue sections.

Cutaneous sensitivity reactions: Skin tests are of limited value in India in view of the fact that they are used only for three diseases, i.e., blastomycosis and coccidioidomycosis (which do not occur in India) and for histoplasmosis, which probably occurs only rarely in India. The specificity of the histoplasmin reaction has recently been disputed by Emmons, Olson, and Eldridge.[2] Moreover, a large-scale skin-sensitivity survey performed by Professor Wahi,[3] did not yield very encouraging results. For this reason, i.e., their non-specificity, their use in a limited number of diseases, and the fact that a large-scale survey had already been done, skin tests were not included in the present series of investigations.

Sputum from 125 patients with roentgenographic and clinical findings suggestive of pulmonary tuberculosis, but with negative microscopic examinations for acid-fast bacilli, have been investigated. Complete bacteriologic and mycologic investigations on these sputum specimens were carried out. Only cases of this type of disease were selected because they are the ones most likely to have been caused by any type of fungi known to attack the bronchopulmonary system.

Of the patients examined, the sputum from 3 proved to be positive for tubercle bacilli.

[1] Kasliwal, R. M., and Andleigh, H. S.: Indian J. M.Sc., 1954, p. 95.
[2] Emmons, C. R., *et al.*: Pub. Health Rep., 1945, *60*, 1383.
[3] Wahi, P. N.: Agra University J. Research (Science), 1952, *1*, 205.

In one, the specimen was positive on culture as well as on microscopy; in the other 2, microscopy was negative but tubercle bacilli were isolated on culture. It is important, therefore, that no sputum should be declared nontuberculous on microscopic examination alone. Even with the concentration method used in the present series, the presence of tubercle bacilli was not detected in 2 of the 125 sputum specimens, i.e., in 1.6 per cent of the patients examined.

Actinomycetes was isolated in 2 cases. In one case, the anaerobic *Actinomyces bovis* was found and, in the other, *Nocardia asteroides* was isolated. Thus, 0.8 per cent of all cases examined were due to the organisms belonging to the anaerobic Actinomyces group and 0.8 per cent to the Nocardia group.

Candida albicans was isolated on repeated culture of the sputum in 2 cases. *Candida albicans* was isolated also from the culture of the bronchoscopic aspirates of these 2 patients. The incidence of bronchopulmonary moniliasis in the present series was 1.6 per cent.

No other fungi which are known to attack the bronchopulmonary system, i.e., *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Geotrichum candidum*, or *Sporotrichum schenckii*, were isolated from any of the cases investigated.

It is concluded that the fungi may play a role in the causation of some instances of pulmonary diseases in India. Thus, pulmonary mycoses must be considered not only in the differential diagnosis of all obscure lung diseases, but also for their coexistence with all sorts of pulmonary infections, particularly in association with pulmonary tuberculosis.

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Editorial

Vocational Rehabilitation in Pulmonary Tuberculosis Today

The two editorials that follow represent somewhat differing points of view on the relative need for vocational rehabilitation in the total management of the patient with tuberculosis today. If our readers wish to express their own positions on this subject, they are encouraged to do so by submitting Letters to the Editor.—The Editor

Once upon a time it was more or less generally agreed by thoracologists that most, if not all, patients who had recovered from pulmonary tuberculosis should lead sheltered lives so that the risk of relapse of the disease would be decreased. This concept stimulated interest in vocational rehabilitation as a part of the tuberculosis control program, and many patients were taught new skills which enabled them to obtain easier and frequently more remunerative jobs. However, this concept of the sheltered life for the patient who has had tuberculosis did not always lead to improvement of occupational opportunities. For example, many young physicians were advised to forget their ambitions to become surgeons or orthopedists and to be content with one of the less strenuous fields in medicine.

It seems to us that developments in the past decade demand a reconsideration of the concept that a sheltered life and therefore vocational rehabilitation are important aspects of the tuberculosis control program. Developments of significance in this regard have been changes in the age group most commonly found to have active tuberculosis; increased efficacy of the treatment of the disease, particularly due to the introduction of antimicrobial therapy and resection of pulmonary lesions; increased education of the American people; and the introduction of more and more machines, so that fewer jobs demand the brute strength of the totally unskilled laborer of yesterday.

We wish to emphasize at the outset that we are considering only *vocational* rehabilitation in this discussion. Other aspects of rehabilitation in general continue to be important aids in the care of patients with tuberculosis and should be made available to everyone who needs such assistance.

Before presenting some data to defend our opinion, we hasten to point out that we are not opposed to teaching people skills that will enable them to earn a better living. In fact, we favor enthusiastically all kinds of adult education for everyone, including ourselves, whether it leads to a better income or to more enjoyment of life. We think, however, that the problem should be faced forthrightly and that the need for vocational rehabilitation should be evaluated objectively from the medical point of view. In other words, we should ask ourselves whether the patient who has had tuberculosis needs training for a better job any more than his fellow citizens, who have not been unfortunate enough to contract the disease, need such training.

To obtain some data that might be of value in considering this problem, we

first analyzed 150 cases in which the diagnosis of tuberculosis had been made recently and consecutively at the Mayo Clinic. We found that the ages, sex, and occupations of these patients were such that only one, a miner, would need vocational rehabilitation after treatment, although others might be taught skills that would benefit them so that they would be able to earn more money afterward. For example, 29 were housewives and would return to keeping house, 21 had already retired from their jobs because of their age, 21 were professional workers, 18 were owners or managers of small businesses, 13 were farmers, and 11 were office workers. Many other skilled and semi-skilled occupations were represented by smaller numbers. One other patient was unable to work because of total blindness and needed vocational rehabilitation for this reason, rather than because of the development of tuberculosis.

Realizing that this group of patients was not representative of all of the tuberculous persons in the United States or even in Minnesota, we next analyzed a series of 279 patients admitted to the Mineral Springs Sanatorium in Cannon Falls, Minnesota, for the first time during the five years, 1952 through 1956. Of these, 152 were males and 127, females. All were 16 years old or more. Eighty-nine of the females were housewives and eight were maids; seven were office workers; five had retired; and the rest were telephone operators, students, sales clerks, teachers, nurses, hospital employees, assembly-line workers, waitresses, or beauticians. While many of these women might have benefited from vocational rehabilitation that would have enabled them to obtain better-paying jobs, we do not believe that such rehabilitation was needed in any instance to prevent relapse of the disease. Among the 152 males, 25 were already retired and 20 were farmers. Ninety were skilled workers, such as physicians, salesmen, mechanics, and barbers. There were 14 unskilled laborers and three whose work exposed them to silica. From a purely medical standpoint, only the last three were in need of vocational rehabilitation.

It is possible that a review of the occupations of patients entering other tuberculosis hospitals would reveal a greater need for vocational rehabilitation than that of these patients, but we have been unable to find data to prove this point.

Neither do we know of any study of the rate of relapse among persons who have had tuberculosis and who returned to various occupations. Such a study would be of great value in determining whether or not our opinion of the need for vocational rehabilitation today is correct.

In conclusion, we would emphasize that we are considering here only *vocational* rehabilitation. The broad concept of "rehabilitation" in general has come to include many aspects of the management of tuberculosis, such as psychotherapy, occupational therapy, financial assistance, therapy for chronic alcoholism or other concomitant diseases, and job placement. These needs continue to a greater or lesser degree, and should be met as adequately as possible with the funds and personnel available. We believe that vocational rehabilitation is needed by only a few tuberculous patients. We submit, therefore, that this type of public assistance, which is limited in availability, should be reserved for those

physically disabled citizens who actually have medical indications for vocational rehabilitation.

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and
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* * *

To a considerable extent we are in agreement with the conclusions drawn by Drs. Carr and Bridge in the accompanying editorial on vocational rehabilitation in pulmonary tuberculosis today. However, we welcome the opportunity to discuss it, for we fear that to many readers of the REVIEW the term "vocational rehabilitation" is synonymous with rehabilitation in general, and it would be regrettable indeed if the many benefits of rehabilitation in its broadest sense were to be denied to patients in our tuberculosis sanatoriums. Moreover, we believe that the data from which their conclusions are drawn regarding vocational rehabilitation per se can scarcely be applied to the United States as a whole. It is true that the mean age of tuberculous patients has increased during the last decade; that the modern treatment of tuberculosis results in recovery which is so nearly complete in a large proportion of cases that the probability of relapse and the need for employment restrictions are greatly reduced; and that with the increase in education and industrialization the segment of the population engaged in strenuous physical activity is ever on the decline. No doubt the time will come when "vocational rehabilitation is needed by only a few patients who have recovered from tuberculosis." We do not believe, however, that such a time is now at hand.

The data on which Drs. Carr and Bridge based the statement quoted above were collected from records of patients at the Mayo Clinic and nearby Mineral Springs Sanatorium in Minnesota. A considerable proportion of these patients in both groups had already reached the age of retirement. Most of the remainder were engaged in occupations not involving any strenuous physical activity. Only a few were in need of *vocational* rehabilitation. They concede, however, that a review of the occupations of patients who enter tuberculosis hospitals in the United States might reveal a greater need for vocational rehabilitation. We are sure that this is true. Certainly, the private patients who come to the Mayo Clinic and those in the prosperous farming community of southern Minnesota can hardly be considered a cross-section of the United States as a whole. These patients cannot be compared with those in tuberculosis hospitals in large metropolitan centers such as New York, Chicago, Detroit, and Philadelphia. Most of these latter patients come from economically depressed areas, are poorly educated and without skills, and they have extensive tuberculosis. Even in these days of miracle drugs and surgical treatment, there are many patients who need special vocational rehabilitation services when they recover from their tuberculosis if they are to compete in today's labor market and yet avoid a relapse.

We have recently analyzed the records of all patients admitted to Chicago State Tuberculosis Sanitarium with some form of tuberculosis during 1956 and 1957. Among a total of 950 patients, the average age was 45.7 years. Of this total, 318 patients (33.4 per cent) were 39 years of age or younger; 449 (47.3 per cent) were between the ages of 40 and 59 years; and 183 (19.3 per cent) were 60 years of age or older. Thus, the great majority of the patients admitted as recently as the last two years were in age groups in which they should return to gainful employment, if this could be brought about. Moreover, the great majority (67 per cent of those with pulmonary tuberculosis) had extensive tuberculosis when admitted to the Sanitarium.

An analysis of the occupations of our patients is interesting. More than 35 per cent of the patients admitted were unskilled laborers less than 60 years of age. Of the others less than 60, approximately 17 per cent were semi-skilled or factory workers; 10 per cent were office workers, clerks, salesmen, students, et cetera; 13 per cent were skilled workers, small businessmen or professional people; 4 per cent were housewives (we have only 30 beds for women); 9 per cent were 65 years of age or older, and the remaining 10 per cent were in the 60- to 64-year age group. In our experience, most of the patients requiring vocational rehabilitation for medical reasons are among the unskilled workers less than 60 years of age. The problems presented by patients in this group tax the ability and resourcefulness of our vocational counselors.

We do agree with Drs. Carr and Bridge that the percentage of patients requiring vocational training per se for medical reasons has unquestionably decreased, chiefly as a result of the more efficacious modern treatment of tuberculosis. However, we wish to emphasize that, as a direct result of this very treatment, we have a new group of patients today who are likely candidates for vocational rehabilitation—patients who would probably not have survived previously, but whose disease today is brought to a status of inactivity or at least of noninfectiousness. These include patients with greatly decreased respiratory reserve, the "good chronics," and the "maximal hospital benefit" patients. It may be pointed out here that more than 70 per cent of our patients require financial help from welfare agencies for varying periods following discharge from the Sanitarium.

Even among tuberculous patients who are not eligible for—or are unlikely to benefit from—vocational rehabilitation, a large number still need counseling, help with job placement, and other services. Rehabilitation is a multidisciplinary process which by definition is "the restoration of the physically handicapped to the fullest physical, mental, social, vocational, and economic usefulness of which they are capable." To this broad definition, Drs. Carr and Bridge have subscribed, and we agree that these needs for tuberculous patients are present today and are likely to continue as long as tuberculosis remains a major medical problem.

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Books

ADVENTURES IN MEDICAL EDUCATION. By G. Canby Robinson. Pp. 338, Harvard University Press, Cambridge, Massachusetts, 1957. Price, $5.00.

Where are the great men in medicine today? Do the great physicians, investigators, college presidents, and philanthropists who contributed so much to the advance of medicine more than a generation ago have current counterparts? These are the thoughts that recur in reading Dr. Robinson's personal narrative of the triumphantly expanding medical science of the earlier years of the century.

The author is well equipped for his task. He says in his preface: "I began to study medicine just when its great advance was gathering momentum and when fundamental changes in medical education were taking place. I was on what might be called the ground floor when these changes began and was in a position to go along with their development almost from the beginning."

Dr. Robinson was a student under Welch, Osler, Halsted, and Kelly at The Hopkins and under Friedrich Mueller at Munich. He was Rufus Cole's first resident at the Hospital of the Rockefeller Institute. He worked with Robert Brookings in the development of the Washington University School of Medicine, and with James Kirkland and Abraham Flexner in planning the Vanderbilt University School of Medicine. With Edward Sheldon he helped bring about the amalgamation of Cornell University Medical College and The New York Hospital. The book is an exciting record of these experiences and offers considerable insight into the network of relationships of the men and institutions of American medicine in the recent past. It also provides some answers to the questions posed above.

With the publication of Abraham Flexner's famous report in 1910, great changes began to sweep over American medical education. The Rockefeller Foundation was then in the first flood of the funds supplied by Mr. Rockefeller, and the Rev. Frederick Gates was repeatedly sounding his warning that the money must be spent before it rolled up and overwhelmed the benefactor. Other men also had great personal wealth at their disposal; men like Robert Brookings, Payne Whitney, and Commodore Vanderbilt. Change was inevitable, resources were at hand, and Johns Hopkins was virtually the only scientific medical school. Replicas soon sprang up at Rochester, Durham, Nashville, and elsewhere; and these schools raided Hopkins again and again for faculty members. To be an assistant professor at The Hopkins was soon to be a department head in one of the new schools. Physicians in full-time academic medicine in those days were assured of opportunities to develop their own programs of teaching and research at an early age. University presidents could work closely with a small group of full-time faculty members, and foundation people could provide great impetus through supplying relatively modest sums for scientific equipment and for construction of laboratories and classrooms.

As late as the 1920's the scientifically trained medical man was a *rara avis*, who stood out from his clinical contemporaries like a black swan or a white crow. He could make intelligent diagnoses and, with luck, sense, and a few simple observations, could often make scientific discoveries of considerable importance. It was possible to be an eminent physician and an expert in such fields as bacteriology, chemistry, and pathology as well. For some, there was even time left over to be a generally cultured man, well-read, and a patron of the arts.

Today, the great men are still here; they are all around us, lost in a crowd. Because the general level of training and competence is higher, outstanding contributions are more difficult to make and, when made, less noticeable. Moreover, as has been well said, today ignorance is a necessary condition of knowledge and specialization is inevitable. As a consequence, all of us must be technicians in some respect and share the management of the patient with others. The profession becomes more and more of a bureaucracy.

The wherewithal to do great things is no longer so easily available either. Money purchases less, and the need has increased overwhelmingly. University administrators spend their energies in rallying financial support from many sources. Foundation executives have to content themselves with gentle stimulation of established institutions, often joining their resources with others', such as the federal government, in support of worthwhile projects. Even the investigator finds he needs to enlist the help of others of his kind to advance research. In *The Organization Man*, William White has voiced amused concern over the multiplicity of authors' names on scientific papers, but some degree of teamwork in scientific investigation has become the norm; the proliferation of knowledge demands it.

Great men are still to be found, but they have less time for contemplation than their predecessors and less autonomy in their decisions. It would seem that greatness today may be achieved only by those who combine creative intelligence with managerial skill. But advances, even though made collectively, are more considerable than ever before and occur on a broader front. The seeming absence of heroic proportions in the leaders today is a small price to pay for the ever-increasing progress that is made.

Dr. Robinson's volume is a valuable record of what lies behind modern medicine and a promise of what may be ahead. It will be a useful primary source for historians for years to come. We are indebted to him, for he has been an accurate reporter of what he lived, felt, and believed, during a crucial period in American medicine.

G. C. Reader
New York, New York

Hormones in Blood. Ciba Foundation Colloquia on Endocrinology. Volume XI. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Pp. 416, Little, Brown and Company, Boston, 1957. Price, $9.00.

The major purpose of this symposium is clearly defined by the chairman, Dr. A. S. Parkes, in his introductory remarks. Because of the greater technical ease of measuring hormonal excretion products in the urine, attention has in recent years been largely diverted to this tangent but, as a consequence of the bewildering number of fractions of hormonal breakdown products obtained, both biologically active and inactive, the picture has become sadly confused. Thus, a plea of "back to the blood" is made and, with this thesis in mind, the participants bring us up to date on the newer methods of measuring hormone levels in the blood and studying transport mechanisms.

Most of the papers deal with thyroid and adrenocortical activity, but new developments in assay and metabolism of hypophyseal hormones, insulin, female sex steroids, and the catechol hormones are also covered. Each speaker is an eminent authority in his field, and each paper is followed by informal discussion by other experts who make comments drawn from their own experience. Of particular interest, the papers on acetylated TSH, the several papers on adrenal and ovarian steroid production and fate in the blood, and the paper on radioisotopically labeled aldosterone in the peripheral blood might be singled out.

This symposium will be primarily of interest to investigators and specialists interested in newer developments in methodology for the assay of endocrine secretions in the blood and for those interested primarily in recent advances in endocrine metabolism in general. It is obviously not primarily intended for the clinician who has merely a casual interest in endocrinology, but even the latter should find this book a useful reference source for some years to come.

BAYARD CLARKSON
New York, New York

GUIDE TECHNIQUE ET TOPOGRAPHIQUE D'EXPLORATION BRONCHOLOGIQUE. By Jean Ionnou, L. Duchet-Suchaux et A. Pinelli. Pp. 110, 66 figures, Masson et Cie., Paris, France, 1956. Price, 1,400 fr.

This brief monograph is a practical guide to the basic investigation and clinical interpretation of the normal and pathologic tracheobronchial anatomy. It is a correlation of anatomy, bronchoscopy, and roentgenography, designed to facilitate the accurate evaluation of pulmonary disease. Illustrations (diagrams, bronchograms, and tomograms) are well selected and beautifully reproduced.

The author states emphatically that methods of investigation should be tailored to the individual patient's need, rather than follow a standard routine of technique for bronchoscopy and bronchography. The indications for and interpretations of bronchography are discussed, and the hazards are enumerated. The last chapter contains a concise, well-illustrated description of the bronchoscopic and bronchographic exploration of the tracheobronchial tree.

The bibliography is divided between references consulted and references cited in the text.

This monograph is a straightforward technical and topographic guide which might be helpful to those with a particular interest in the delineation and interpretation of the anatomy and pathology of the tracheobronchial tree.

KEITH MERRILL, JR.
Brookline, Massachusetts

BOOKS RECEIVED

SOCIAL STATUS AND PUBLIC HEALTH. By Ozzie G. Simmons. Pp. 34, Social Science Research Council, New York, 1958. Price, 50 cents.

THE PASTEUR FERMENTATION CENTENNIAL 1857–1957. A Scientific Symposium. Pp. 207, Chas. Pfizer & Co., Inc., New York, 1958.

TUBERCULOSIS IN ANIMALS AND MAN. By John Francis. Pp. 357, Cassell and Company Limited, London, 1958. (The Williams & Wilkins Co., Baltimore, exclusive U.S. agents). Price, $18.00.

PUBLIC EXPOSURE TO IONIZING RADIATIONS. By the Program Area Committee on Radiological Health of the Technical Development Board of the American Public Health Association. Pp. 55, The American Public Health Association, Inc., New York, 1958.

CHIRURGIE D'EXÉRÈSE DANS LA TUBERCULOSE PULMONAIRE. By D. Honoré. Pp. 216, Masson et Cie, Paris, 1958. Price, 3,300 fr.

EFFECTS OF SOCIAL AND CULTURAL SYSTEMS IN REACTIONS TO STRESS. By William Caudill. Pp. 34, Social Science Research Council, New York, 1958. Price, 50 cents.

HOW TO LIVE WITH DIABETES. By Henry Dolger and Bernard Seeman. Pp. 192, W. W. Norton & Company, Inc., New York, 1958. Price, $3.50.

CARDIAC PROBLEMS FOR CHEST PHYSICIANS. A NAPT Symposium. Pp. 39, National Association for the Prevention of Tuberculosis, London, 1958. Price, $1.25.

THE CEREBROSPINAL FLUID—PRODUCTION, CIRCULATION, AND ABSORPTION. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Pp. 335, Little, Brown and Company, Boston, 1958. Price, $9.00.

A PRACTICAL MANUAL ON THE MEDICAL AND DENTAL USE OF X-RAYS WITH CONTROL OF RADIATION HAZARDS. By Richard H. Chamberlain and Robert J. Nelsen. Pp. 31, The American College of Radiology, Chicago, 1958. Price, 25 cents.

American Trudeau Society

Medical Section of the National Tuberculosis Association

RECOMMENDED STANDARDS FOR HOME CARE OF PATIENTS WITH TUBERCULOSIS

A Statement of the Committee on Therapy

The advantages and disadvantages of prolonged hospitalization and of home care for patients with tuberculosis are well known. It is the opinion of this American Trudeau Society committee that a plan incorporating the features described below should provide adequate care for selected patients.

1. *Preliminary hospitalization:*

This committee believes hospitalization is an essential part of the treatment of all forms of active tuberculosis. All patients should be urged to accept hospitalization as soon as the need for treatment is established. Hospitalization should continue until:

A. Diagnostic procedures adequate for the evaluation of the entire patient and his disease have been completed

B. Chemotherapy has been instituted and the patient's tolerance to the drugs prescribed has been determined

C. Symptoms, if any, have been controlled

D. Communicability of the disease is believed to have been adequately diminished for the patient's circumstances

E. It has been determined that home conditions are adequate for care of the patient, and the patient has demonstrated an attitude of trustworthiness and cooperation

F. It has been determined that the family is not only capable but is *desirous* of caring for the patient and will make the sacrifices which home care requires

G. The patient has been well instructed about his disease and its treatment including the development of good dietary habits and good habits of personal hygiene

H. Uninterrupted medical care is assured, including regular visits to the physician or house calls if indicated.

2. *Medical care at home:*

Adequate medical attention requires regular and frequent visits between patient and physician. Medical house call services should be available for care of acute intercurrent illnesses. The status of the tuberculous infection should be re-evaluated following such intercurrent illnesses. Whenever possible the same physician should continue with each patient over a period of years to ensure a consistent long-term chemotherapeutic treatment program. When more than one physician is involved in the care of a patient or when the patient is being transferred from the care of one physician to another, responsibility for maintaining the patient on continuous, adequate treatment for the tuberculosis must be prearranged and clearly defined. In the ideal situation the physician in charge during the preliminary hospitalization should be in charge of the home-care program. Home care does not necessarily shorten the total period of disability. The physician supervising home care should discourage premature return to work.

3. *Recurring hospital readmissions:*

Patients under treatment at home should have available to them the diagnostic and consultative services of the modern hospital or clinic. Routine periodic readmissions to the hospital for a few days may be necessary. Re-evaluation by roentgenographic, bacteriologic, clinical, and laboratory procedures should be followed by presentation at a staff conference. Included in this conference group should be surgeons who would help to determine when and if surgical procedures might be undertaken.

4. *Special services for home-care patients:*

Social workers, occupational therapy workers, school teachers, rehabilitation workers, and other patient counsellors provide many advantages to hospital care. When needed, these services and those of the public health nurse should be available to patients at home.

5. *The private physician and home care:*

A. It should be the aim of any program to delegate to the patient's personal private physician as much of the responsibility for medical care as possible. A private physician well indoctrinated in the care of tuberculosis could supervise the patient's home care. If the patient's private physician does not conduct long-term outpatient treatment of tuberculosis, he should be kept well informed of the patient's progress, consulted with in the event of intercurrent illness, and take over complete care when the treatment of the tuberculosis has been completed.

B. Under some circumstances private home care and private office care of medically indigent patients at the expense of public funds may be preferable to institutional care (or "clinic" care) when private physicians well experienced in the modern chemotherapy of tuberculosis are available.

C. It is essential that the attending physician and public health officials collaborate in long-term management of a potentially communicable disease such as tuberculosis.

H. Dumont Clark
H. Corwin Hinshaw
Felix A. Hughes, Jr.
Edna M. Jones
James W. Raleigh
Col. James A. Wier
William R. Barclay, *Chairman*

ANTIMICROBIAL THERAPY OF TUBERCULOSIS

A Statement of the Committee on Therapy

The Committee on Therapy has reviewed the statement[1] prepared in 1955, "Antimicrobial Therapy of Tuberculosis," and approves the general recommendations on chemotherapy contained in that report. The principal change that has occurred in the attitude toward therapy of tuberculosis in the past several years has been a loss of complacency; a change in the sense of satisfaction in achieving excellent results in 70 to 90 per cent of cases of tuberculosis, even in the face of advanced disease, to a sense of dissatisfaction with the 10 to 30 per cent of treatment failures. There is now a striving to achieve 100 per cent good results in treatment through the better or more intelligent use

[1] American Trudeau Society: Am. Rev. Tubere., 1955, *72*, 408.

of the drugs that we now have. Some of the newer concepts in treatment, many still unproved, may be summarized as follows:

Streptomycin:

1. There is increasing support for the view that streptomycin in a dosage of 1 gm. daily is more effective than when used intermittently, particularly in combination with isoniazid, for the treatment of the patient with more severe disease.

2. Duration of administration of daily streptomycin has been continued for one month to a year or more, then changed to intermittent dosage.

3. Using the larger doses of streptomycin, an increased incidence of ototoxicity has again occurred, being more pronounced in patients of the older age group or in those with renal impairment.

Isoniazid:

Isoniazid is considered to be the most effective drug used in the treatment of tuberculosis. In adequate dosage, combined with one or more of the other drugs in use, it promises the best results of treatment available today. Certainly past experience indicates that most patients treated with isoniazid in standard dosage, 300 mg. per day, with streptomycin or PAS, will do well. In recent years it has been demonstrated that isoniazid is metabolized in the human to inactive forms, the principal one being acetyl isoniazid. As measured by bioassay techniques, the acetylated form is therapeutically not active against the tubercle bacillus. Inactivation takes place at varying rates from one individual to another, in some to such a degree that no concentration of active isoniazid is present in the serum as measured by bioassay. Increasing the dose of isoniazid will elevate the serum concentrations of free active isoniazid. In a few patients, administration of extremely high doses may still not result in adequate concentrations.

Determination of blood serum concentrations of active isoniazid may become very important for clinical guidance if work now in progress confirms current theories. As the technique of bioassay is not readily available in all laboratories, and as its clinical usefulness is not completely confirmed, three general courses are open to physicians treating tuberculosis:

1. Treating with standard dosages (300 mg. per day) and accepting the fact that in some individuals this dosage may be inadequate

2. Treating all patients with a higher dose (12 mg. per kg. per day) plus pyridoxine, and accepting that in few individuals this still may be inadequate and accepting the factors of increased toxicity and cost

3. Treating more seriously ill patients with daily streptomycin and high-dosage isoniazid with or without PAS early in course until conversion of sputum; then reverting to more conventional dosage.

Para-aminosalicylic acid (PAS)—(Amino-salicylic acid, USP XV):

1. In an effort to produce less toxic, more palatable forms of this drug, many different products have been manufactured. Comparison of blood serum concentrations indicates a moderate variation in the absorption rate of the different forms of PAS and likewise in the rate of disappearance of the drug from the blood stream.

2. It is known that this drug is metabolized in the body in a way somewhat similar to isoniazid. The clinical significance of this fact is under study but has not been clearly determined at the present time.

3. Attention is called to the fact that many patients do not take the prescribed dosage of this drug. Simple qualitative tests for PAS in the urine have made it possible to check

the percentage of patients actually taking the drug. This is particularly important in outpatient therapy.

Other drugs:

Recent reports of the committee[2-4] have been devoted to the subjects of pyrazinamide, cycloserine, and steroid therapy. Streptovaracin, kanamycin, and thiocarbanidin cannot be recommended for use in the treatment of tuberculosis at the present time except under conditions of experimental control.

General remarks on chemotherapy:

At the present time it must be concluded that the best drug treatment for tuberculosis consists of combinations of the three standard drugs, streptomycin, PAS, and isoniazid, used for long periods of time, 18–24 months. The use of isoniazid alone as initial treatment for active tuberculosis is not recommended by this committee. Studies comparing the therapeutic effectiveness of isoniazid alone with isoniazid plus PAS in the treatment of minimal and moderately advanced noncavitary tuberculosis are now in progress. Thus far, no conclusive evidence has been presented which proves that isoniazid used alone is equal in therapeutic effectiveness to isoniazid combined with other antituberculosis agents. Other combinations, including pyrazinamide, cycloserine, and viomycin, are recommended when combinations of other standard drugs cannot be used for one reason or another.

The statements of the committee[5, 6] published in 1955 concerning the chemotherapy of tuberculosis in childhood and the chemotherapy of genitourinary tuberculosis have been reviewed and still contain valid recommendations for therapy.

H. DUMONT CLARK
H. CORWIN HINSHAW
FELIX A. HUGHES, JR.
EDNA M. JONES
JAMES W. RALEIGH
COL. JAMES A. WIER
WILLIAM R. BARCLAY, *Chairman*

[2] AMERICAN TRUDEAU SOCIETY: Am. Rev. Tubere., 1957, *75*, 1012.
[3] AMERICAN TRUDEAU SOCIETY: Am. Rev. Tubere., 1957, *75*, 1016.
[4] AMERICAN TRUDEAU SOCIETY: Am. Rev. Tubere., 1957, *76*, 708.
[5] AMERICAN TRUDEAU SOCIETY: Am. Rev. Tubere., 1955, *72*, 412.
[6] AMERICAN TRUDEAU SOCIETY: Am. Rev. Tubere., 1955, *72*, 413.

NOTICES

The following dates and locations of the next two annual meetings of the National Tuberculosis Association and the American Trudeau Society have been selected and approved:

1959—Chicago, Illinois—May 24–29
1960—Los Angeles, California—May 15–20

NTA FELLOWSHIPS

The Medical Section of the National Tuberculosis Association, the American Trudeau Society, provides a limited number of fellowships to promote the training of clinicians, medical teachers, and scientific investigators in the field of tuberculosis and respiratory diseases. Awards are open to citizens of the United States for work within this country.

Candidates holding the degrees of M.D., Ph.D. or Sc.D., are eligible for awards making possible continuation of graduate study in the field of respiratory diseases in an approved hospital or medical center. Such studies may be oriented toward teaching or research. Residency in an approved hospital under such a fellowship will be credited by the American Board of Internal Medicine toward certification in internal medicine and pulmonary diseases.

Predoctoral fellowships are also offered to graduate students who hold a bachelor's degree and are working on a research project for an advanced degree other than an M.D.

Each applicant must have the approval of the head of the department under whom he expects to work. All awards are determined by individual circumstances and are paid directly to the Fellow on a quarterly basis. Fellowships are granted for one year. Not more than two renewals will be considered. Fellowship applications must be received by December 1. Appointments may begin on any date at the convenience of the applicant.

TRUDEAU FELLOWSHIPS

A few fellowships at a higher level of training and award are offered to specially qualified candidates with an M.D. degree who have been assured of a continued teaching or research appointment upon completion of training. Trudeau Fellowships are awarded for one year but may be renewed up to a total period of four years.

Further particulars concerning fellowships may be obtained upon request from:

The Director of Medical Education, American Trudeau Society, % The Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia 47, Pennsylvania.

ANNUAL MEETING OF THE AMERICAN TRUDEAU SOCIETY

The Medical Sessions Committee *INVITES SUBMISSION OF PAPERS* on all scientific aspects of tuberculosis and nontuberculous respiratory and cardiopulmonary diseases for presentation at the *1959 annual meeting in Chicago, Illinois, May 25–27.*

Abstracts

1. Abstracts of papers to be offered for presentation should be submitted before January 7, 1959, to the Chairman of the Medical Sessions Committee. *Seven copies* are required for distribution to committee members.

2. Abstracts should be limited to a 300-word summary including important data *and conclusions.* Charts and tables should be attached to aid in the selection of papers. Ab-

stracts selected for presentation at the annual meeting will be published in THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES.

3. The names, academic degrees, titles, and complete addresses of the senior author and coauthors should be included in each abstract.

4. All abstracts will be reviewed by the Medical Sessions Committee. Selection will be largely based on the areas of interest suggested by you and others receiving this invitation.

5. Those wishing to present subjects of a confidential nature from the armed forces or other sources should first clear the material through official channels.

6. Authors will be notified by March 1, 1959, if their papers have been accepted for presentation.

7. Papers presented at the annual meeting must be ORIGINAL contributions NOT PREVIOUSLY PRESENTED OR PUBLISHED. Medical papers presented at the meeting may be submitted to THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES by the author if he so desires.

Suggestions

The Medical Sessions Committee is particularly anxious to build the 1959 program around your special interests. A memorandum suggesting subjects and speakers would be welcome and should be sent to the Chairman by October 15, 1958.

H. WILLIAM HARRIS, M.D., *Chairman*
Medical Sessions Committee
American Trudeau Society
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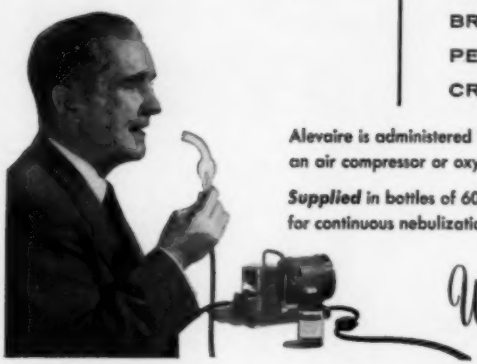

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Recent references: The Laryngoscope LXVIII:25-31 (January) 1958. Transactions of the American Academy of Ophthalmology and Otolaryngology 62:178-188 (March-April) 1958.

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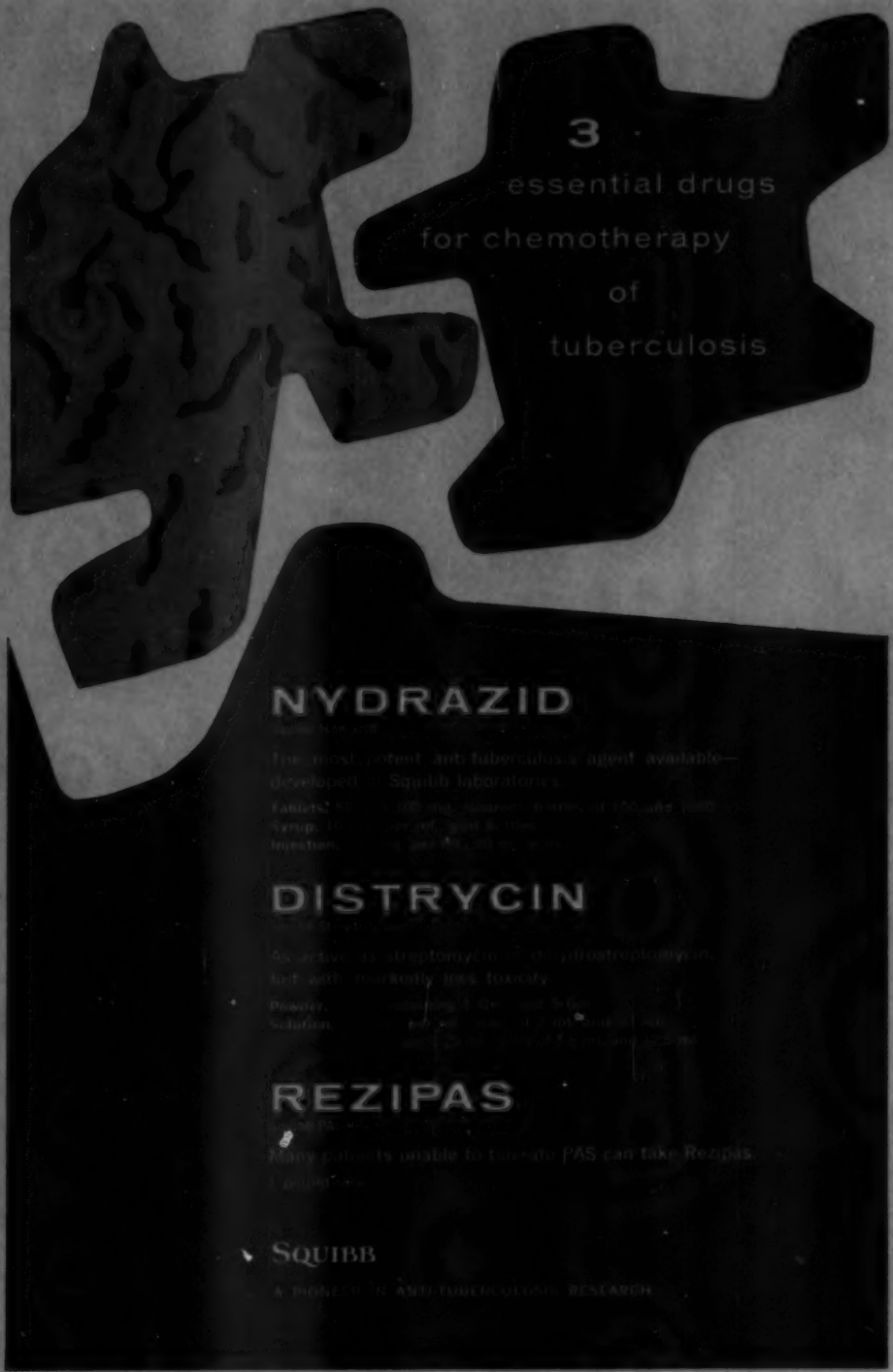
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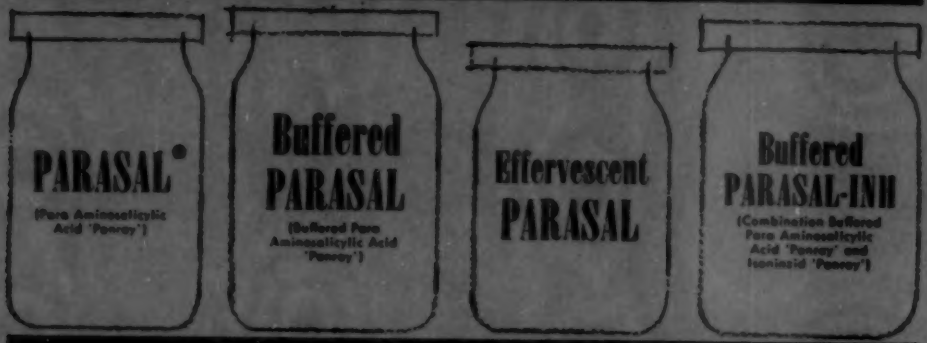

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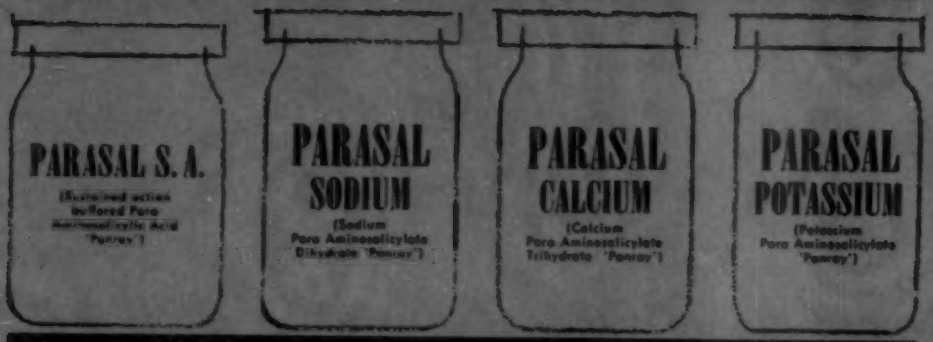

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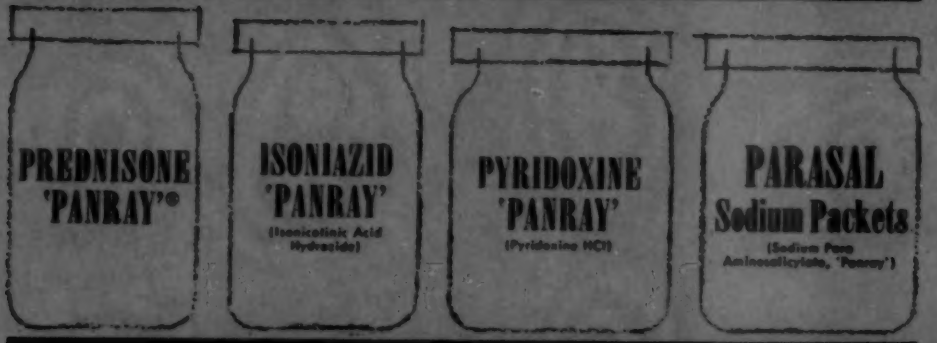

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